REPUBLIC OF KENYA

KENYA NATIONAL MEDICINES FORMULARY

1st Edition 2023

Kenya National Medicines Formulary

Detailed Information on the Medicines included in KEML 2023

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Table of Contents

Foreword

The Kenya Government is implementing universal health coverage (UHC) as one of the priorities of the Kenya Kwanza manifesto. UHC aims to ensure that all citizens have access to safe, effective, quality essential health care services, which includes affordable essential health products and technologies (HPT) without suffering financial hardship. UHC is anchored in the Kenya Health Policy 2014-2030 and includes primary health care. The focus of UHC is not only on preventing and treating disease and illness but also on improving the population's general wellbeing and quality of life.

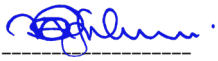
The Health Products & Technologies Supply Chain Strategy 2020-2025 identified the lack of a National Formulary in Kenya as a major gap that needs to be addressed. The National Medicines and Therapeutics Committee (NMTC), which was inducted in September 2019, has 12 terms of reference, one of which is the development of a National Formulary.

Inauguration of a National Formulary in Kenya will be a milestone in guiding the various health care facilities on developing formularies to guide good prescribing practices. Though many hospitals in both the public and private sectors have developed formularies that guide prescribing habits and clinical practice, a National Formulary has not been in place.

The Kenya Essential Medicines List (KEML) 2019 was used as the main backbone in developing the Kenya National Medicines Formulary (KNMF) 2023. Detailed monographs have been developed for all medicines in the formulary.

It is envisioned that the National Formulary will have many uses, including guiding appropriate use of medical products, which include antimicrobials, control of prescribing patterns, and levels of practice. It is my hope that this National Formulary, once implemented, will guide health care facilities in customizing utilization of medical products and clinical practice in the various specialty areas.

The Ministry of Health (MOH) acknowledges the commitment and dedication of many individuals who contributed their time and expertise at the various stages of development of the KNMF. This includes the technical guidance and financial support provided by United States Agency for International Developement (USAID) through the USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) program that is implemented by Management Sciences for Health (MSH).



Nakhumicha S. Wafula
Cabinet Secretary
Ministry of Health

Acknowledgements

The first Kenya National Medicines Formulary (KNMF) is the collaborative work of the Technical Working Group (TWG) members from National and County levels that were appointed to develop the document. I wish to acknowledge and sincerely thank all contributors, including MOH officers in various directorates, departments, and divisions; various professional associations that reviewed categories of medicines in their areas of specialty; the Directorate of Health Products & Technologies that spearheaded the development process and acted as the TWG Secretariat; and the consultant who made this KNMF a reality.

Finally, we would also like to gratefully acknowledge the technical guidance and financial support provided by the United States Agency for International Development through the USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) program that is implemented by Management Sciences for Health. They made this inaugural KNMF a reality.

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Executive Summary

The Health Products and Technologies Supply Chain Strategy 2020-2025, under its Strategic Objectives 2.1.6 and 2.8.6, states that there is need to develop a National Formulary for all essential medicines and selected supplies to guide the health system. The formulary shall ensure that HPT are responsive to the priority needs of Kenyans, in line with the concept of essential HPT, and to also guide the implementation of rational use of HPT. MOH, through the NMTC, constituted a multidisciplinary team of professionals, namely, the KNMF Technical Working Group (TWG), to spearhead developing the KNMF. The KNMF TWG convened a series of meetings and discussions with a variety of medical specialists to obtain this final product.

The formulary has been developed in four sections: front matter, medicine monographs, appendices, and index. It has thirty-five (35) categories that are similar to the KEML 2023 . The monographs include details such as name of medicine, Anatomical Therapeutic Category (ATC) code, formulation, level of use, indications and dose, contraindications, precautions such as hepatic and renal impairment, use in pregnancy & breastfeeding, adverse effects, drug interactions and other relevant notes.

The KNMF has retained the categorization of antibiotics into access, watch, and reserve (AWaRe) classes that were introduced in KEML 2019 (and retained in KEML 2023) to guide the rational use of antibiotics, in line with global guidance provided by the World Health Organization (WHO). The AWaRe classification for antibiotics is intended to incorporate antibiotic stewardship to reduce and contain antimicrobial resistance (AMR) globally.

An effective formulary system is useful for priority setting because careful selection of a limited range of essential medicines results in better quality of care, better medicine management (including improved quality and availability), and more cost-effective use of health resources. It also helps identify priority health interventions.

The use of an essential medicines list (EML), and hence a medicines formulary, results in more efficient procurement, storage, distribution, inventory management, and record keeping because health facilities focus on a smaller range of items.

Use of an EML also enables prescriber and dispenser training and practice to be more focused and easier to deliver; production of more focused medicine information; minimizing irrational treatment alternatives; and better recognition of adverse drug reactions.

In addition, an effective formulary system results in focused education efforts on fewer well-known medicines, improved patient knowledge on medicine use, and increased treatment adherence.

The KEML and KNMF should be used as a basis for effectively regulating all activities involving medicines (including import, export, local production, registration, levels of distribution/use, quality monitoring, post-market surveillance, pharmacovigilance, prescribing, and dispensing. In addition, these documents should be used as the focus of surveys, studies, and operational research as well as monitoring and evaluation by the NMTC and institutional medicines and therapeutics committees (MTCs).

The KEML and its companion document, the KNMF, are a cornerstone of the national health care system and a key component of both the national health and national pharmaceutical policies. These are important tools and references for managing common health conditions in the country, as well as managing and utilizing medicines at national, county, and institutional (health facility) levels.

It is envisioned that these documents will be used as a basis for prioritizing investment of available health care finances and, together with accurate quantification of HPT needs, for estimating required annual medicine supply budgets *at all levels of the health care system*. They also form the basis for selecting medicines for implementing the health benefits package as defined by the UHC benefits panel as well as the basis for expanding coverage or reimbursement of medicine costs. UHC delivery is through a social health insurance model that uses a UHC essential health benefits package. One of the packages required is a pharmaceutical benefits package to enhance availability and appropriate use while containing costs. This requires several guiding documents, national clinical guidelines, essential HPT lists, and the National Formulary. Kenya, being a free economy, does not allow control of medicine prices, hence medicine prices are not indicated in the KNMF. Currently, an HPT price reference system is under development, which will be a more suitable reference point for medicine prices in future National Formulary editions.

The inclusion of Anatomical Therapeutic Chemical (ATC) Classification System codes, a system maintained by WHO that assigns unique codes to medicines according to the organ or system the medicines work on or how the medicines work, will facilitate drug utilization monitoring and research.

I urge all relevant health professionals to make the best use of the KNMF in their daily work and provide feedback on its use and suggestions for improvement and future revisions.

Dr. Patrick Amoth, EBS

Ag. Director General for Health

Abbreviations & Acronyms

ACEI	Angiotensin-Converting-Enzyme Inhibitor
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
amp	Ampoule
AMR	Antimicrobial Resistance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
ART	Antiretroviral Therapy
AWaRe	Access, Watch, and Reserve
APTT	Activated Partial Thromboplastin Time
AUC	Area Under The Curve
AV	Atrioventricular
BCG	Bacillus Calmette-Guérin
BSA	Body Surface Area
CAPD	Continuous Ambulatory Peritoneal Dialysis
CBC	Complete Blood Count
CCB	Calcium Channel Blocker
CDAD	*Clostridium Difficile*-Associated Diarrhea
CKD	Chronic Kidney Disease
Cl	Chloride
CLL	Chronic Lymphocytic Leukaemia
CMV	Cytomegalovirus
CNS	Central Nervous System
CrCl	Creatinine Clearance
CTCAE	Common Terminology Criteria for Adverse Events
CVC	Central Venous Catheter
CYP	Cytochromes P450
D	Day
dL	Decilitre
DMARDs	Disease Modifying Agents Used in Rheumatic Disorders
e/c	Enteric Coated (Tablet)
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EN	Enteral Nutrition
ESRD	End-Stage Renal Disease
f/c	Film Coated (Tablet)
FBF	Fortified Blended Food
FDA	Us Food And Drug Administration
FDC	Fixed-Dose Combination
g	Gram
GERD	Gastroesophageal Reflux Disease

GI	Gastrointestinal
GCSF	Granulocyte Colony Stimulating Factor
GIT	Gastrointestinal Tract
G6PD	Glucose-6-Phosphate Dehydrogenase
HBV	Hepatitis B Virus
HCl	Hydrochloride Salt
HCTZ	Hydrochlorothiazide
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HPT	Health Products and Technologies
IM	Intramuscular
INR	International Normalised Ratio
i/r	Immediate Release
IU	International Unit
IV	Intravenous
KEML	Kenya Essential Medicines List
kg	Kilogram
kcal	Kilocalorie
KNMF	Kenya National Medicines Formulary
L	Litre
LCT	Long-Chain Triglyceride
LDL	Low-Density Lipoprotein
LOU	Level Of Use
MAM	Moderate Acute Malnutrition
MAOI	Monoamine Oxidase Inhibitor
Max	Maximum
MBq	Megabecquerel
mCi	Millicurie
MCT	Medium-Chain Triglyceride
MDR-TB	Multidrug-Resistant Tuberculosis
mEq	Milliequivalent
mg	Milligram
MI	Myocardial Infarction
min	Minute
mL	Millilitre
mmol	Millimole
MMR	Mumps, Measles, Rubella
MOH	Ministry of Health
mOsm	Milliosmole
m/r	Modified (Controlled, Delayed, Prolonged, Slow) Release
MRSA	Methicillin Resistant *Staphylococcus Aureus*
MSH	Management Sciences for Health
MTaPS	Medicines, Technologies, and Pharmaceutical Services Program

MTC	Medicines and Therapeutics Committee
MU	Mega (Million) Units
MUAC	Mid-Upper Arm Circumference
NMTC	National Medicines and Therapeutics Committee
NSAIM	Non-Steroidal Anti-Inflammatory Medicine
ORS	Oral Rehydration Salt
PCV	Polysaccharide Conjugated Vaccine
PN	Parenteral Nutrition
PPH	Postpartum Hemorrhage
ppm	Parts Per Million
PT	Prothrombin Time
PUV	Psoralen and Ultraviolet-A Light
PVERS	Pharmacovigilance Reporting System
ReSoMal	Rehydration Solution For Malnutrition
RDA	Recommended Dietary Allowance
RUSF	Ready-To-Use Supplementary Food
RUTFs	Ready to use Therapeutic Foods
SAM	Severe Acute Malnutrition
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
SC	Subcutaneous
SCAR	Severe Cutaneous Adverse Reaction
SJS	Stevens-Johnson Syndrome
SLE	Systemic Lupus Erythematosus
SPECT	Single Photon Emission Computed Tomography
SPF	Sun Protection Factor
SSRI	Selective Serotonin Reuptake Inhibitor
TB	Tuberculosis
TPN	Total Parenteral Nutrition
TT	Tetanus Toxoid
TWG	Technical Working Group
UHC	Universal Health Coverage
ULN	Upper Limit of Normal
USAID	United States Agency for International Development
WBC	White Blood Cell
WHO	World Health Organization
WHZ	Weight for Height Z-Score
w/w	Weight by Weight

Kenya National Medicine Formulary Background Information

Medicines play a crucial role in preventing and treating diseases. When used correctly, they offer simple and cost-effective solutions to many health problems. Today, many people have little or no access to safe and effective drug therapies and may be at risk of serious health problems due to treatment with ineffective, poor quality products or incorrect and irrational use of medicines.

USAID MTaPS, in collaboration with Kenya's NMTC and other stakeholders, revised the KEML in 2019 and incorporated AWaRe categorization of antibiotics. The AWaRe categorization has been retained in KEML 2023. AWaRe is intended to help monitor the use of antibiotics, particularly those belonging to the watch and reserve categories, and enhance antimicrobial stewardship, which is a key strategic objective of the WHO Global Action Plan on AMR 2015 and Kenya's National Action Plan on AMR 2017-2022.

Formularies are useful tools in solving some drug therapy problems because they provide impartial drug information to counteract biased promotional activities or fill the gap where access to accurate and up-to-date information is limited; promote the appropriate use of safe, effective, and good quality medicines; help eliminate unsafe, ineffective, or poor-quality medicinal products by identifying effective and safe medications; and support cost-effective utilization of drug budgets and improve access to essential medicines.

MOH, in collaboration with the USAID MTaPS program and other partners, worked together to develop this inaugural KNMF. The KNMF describes medicines, including antimicrobials, that are available for use in Kenya and provides information on indications, dosage, length of treatment, adverse effects, interactions, precautions, contraindications, and useful notes. This will help guide appropriate prescribing of medicines in health care settings, leading to better patient outcomes.

Development Process

MOH constituted a TWG comprising members from the national and county levels and the private sector. The TWG worked with the USAID MTaPS technical lead, the consultant, and the secretariat to develop content for the KNMF. The TWG, by consensus, agreed to develop monographs for medicines listed in the KEML 2019 and updated to align to KEML 2023. Input from the TWG was collated into a draft formulary and shared with experts from various professional associations. Feedback received from the reviewers was validated by the TWG.

Rationale for including Medicines in the KEML

KEML 2023 was adopted from the WHO Model Lists (22nd edition for adults and 8th edition for children of 2019) and various current national guidelines for specific conditions which represent the best current therapeutic practice in the priority conditions covered. It is based on the concept of essential medicines, defined by WHO as:

- Those medicines that meet priority health care needs of the population
- Medicines carefully and systematically selected using an *evidence-based process* with due consideration of:
  - Public health relevance
  - Clear evidence on efficacy and safety
  - Comparative cost-effectiveness
- Medicines meant to be always available in a functioning health care system:
  - In adequate amounts
  - In appropriate dosage forms
  - With assured quality and adequate information
  - At an affordable price for the individual and community

Medicines included in the KEML are those with proven efficacy and safety, in order to meet the needs of the majority of the population. Unnecessary duplication of medicines and dosage forms is avoided. Only those medicines for which adequate scientific data are available from controlled clinical trials and/or epidemiological studies and for which evidence of performance in general use in a variety of settings has been obtained were selected. Newly released medicines are included if they have distinct advantages over medicines that have been in use longer.

The international nonproprietary names (generic name) of medicines are used and the cost/benefit ratio of medicines are considered in selecting medicines for inclusion on KEML. Fixed-dose combinations (FDCs) are only acceptable when the dosage of each ingredient meets the requirements of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, compliance, or cost.

When two or more medicines appear to be similar, preference is given to medicines:

- That have been most thoroughly investigated

» With the most favourable pharmacokinetic properties

» For which reliable local manufacturing facilities exist

Presentation of Information in the KNMF

The formulary has been developed in four sections: front matter, medicine monographs, appendices, and index. The formulary has 35 categories that are similar to KEML 2023.

The monographs include details such as name of medicine, ATC code, formulation, LOU, indications and dose, contraindications, precautions (such as hepatic and renal impairment), use in pregnancy and breastfeeding, adverse effects, interactions with other medicines, and notes. The format for section 33 (Preparations for Clinical Management of Nutrition) is different from the rest of the document.

In this document, a NEONATE refers to a child under 28 days of age; an INFANT refers to a child under 1 year; a CHILD refers to any person under 18 years; an ADOLESCENT refers to any person between 13 and 18 years; an ADULT refers to any person above 18 years; and ELDERLY refers to any person above 60 years of age.

Classification of Levels of Health Care Delivery/LOU

Kenya's health care system is structured in a hierarchical manner that begins with primary health care, with the lowest unit being the community, and then graduates, with complicated cases being referred to higher levels of health care.

The LOU in the KNMF indicates the **lowest level** of the health care delivery system at which each particular medicine may reasonably be expected to be appropriately distributed, stored, prescribed, and dispensed.

The current levels are as follows:

» Level 1: Community health services

» Level 2: Dispensary/clinic

» Level 3: Health centre

» Level 4: Primary hospital (sub-county hospital)

» Level 5: Secondary hospital (county referral hospitals)

» Level 6: Tertiary hospital (national [teaching and] referral hospitals)

The Formulary System

The formulary system consists of periodically evaluating and selecting medicines for the EML/formulary, maintaining the formulary, and providing information in a suitable manual or list. Essential medicines and formulary systems are the backbone of MTCs. The formulary improves patient care at decreased cost through improved selection and rational medicine use while improving efficiency within procurement and inventory management programs.

The formulary should be revised periodically to reflect the current judgment of medical staff. Selecting medicines for the formulary is the most important function of the formulary system. The process is multifactorial and considers the following:

» Medicines should be selected based on the needs of the community; they should treat locally identified diseases and conditions.

» Medicines selected for the formulary are "medicines of choice."

» The formulary list should have a limited number of medicines; duplication of agents that have therapeutic equivalence should be avoided.

» International nonproprietary names (i.e., generic names) should be used.

» Combination (fixed dose) products should be used only in specific, proven conditions (e.g., to treat TB).

» Medicines need to be selected based on explicit criteria that include proven efficacy, relative efficacy, effectiveness, safety, quality, cost, and cost-effectiveness

» The formulary must be consistent with approved national standard treatment guidelines.

» Medicines should be restricted to appropriate practitioners.

» Health system personnel must be available to manage medicines.

» Financial resources must be available.

The formulary maintenance process depends on two key components:

» Additions and deletions of medicines

» Therapeutic medicine class reviews

The MTC adopts a standard policy and procedure for decision making on medicine deletion and addition. The method adopted is transparent. Systematic review of a class of medicines allows for the entire formulary to be reviewed over a two-to-three-year period. Regular MTC meetings, where decisions on additions or deletions of medicines are taken, ensure that the formulary system is maintained on a continuous basis.

Review considers the following:

» New medicines that have an advantage over the current selections are considered for inclusion.

» Medicines that are no longer used or lack sufficient evidence of efficacy, safety, and quality are recommended for deletion.

» Medicines that no longer meet the criteria for being cost-effective are evaluated and deleted when an acceptable alternative is identified.

» Adding a new medicine leads to deleting a similar medicine on the formulary or considers robust evidence and local treatment guidelines.

» Deletion, rectification, or amendment of those with medicine use problems.

The steps followed in reviewing the formulary include:

» Requesting addition of a medicine to the formulary by a prescriber or pharmacist using a standard form, such as the formulary amendment proposal form (appendix 1)

» Obtaining credible and unbiased medicine information resources, including primary literature, international newsletters, standard treatment guidelines, textbooks, and internet sources

» Evaluating according to established criteria

» Writing the medication monograph

» Developing formulary recommendations by the reviewer of the application

- Obtaining expert opinions and recommendations from knowledgeable and respected prescribers and pharmacists; opinions should complement—not replace—the information provided in a medicine information search
- Presenting the new information at the MTC meeting and conducting a vote
- Disseminating the results of the evaluation and MTC's recommendations and actions to the health care staff

Monitoring KNMF Utilization

Terms of Reference of the NMTC

1. Develop policies on clinical governance, rational use of essential medicines, and health products and technologies (EHPT)
2. Develop standards, including guidelines and standard operating procedures
3. Develop/review and update all relevant appropriate-use guidelines: National Clinical Management and Referral Guidelines, National Formulary, national essential HPT lists, and other specific/specialized treatment guidelines and protocols
4. Collaborate with departments/divisions/units involved in the introduction of disease-based or vertical programs in which selection and use of medicines and other EHPT is a significant component
5. Facilitate medicine and other EHPT education regarding appropriate use and safety for health workers, consumers, and county and national agencies
6. Support county and hospital MTCs by developing and disseminating guidelines, training materials, and capacity building
7. Participate in the development, review, and revision (as necessary) of pre- and in-service continuous professional education content on use of medicines and therapeutics
8. Review research findings related to HPT and recommend appropriate interventions
9. Advocate for the role of, importance of, and support for NMTC, including a sustainable mode of funding

Indicators to Monitor Rational Use of Medicines

The following indicators have been adapted from the monitoring and evaluation matrix in the HPT Supply Chain Strategy 2020-2025 and WHO/DAP 93.1, How to investigate drug use in health facilities. Furthermore, indicators 6 and 7 support implementation of the Kenya National Action Plan on Prevention and Containment of Antimicrobial Resistance (2017-2022) and accompanying Antimicrobial Resistance National Action Plan Monitoring & Evaluation Framework (July 2021).

Indicator	Indicator definition
Proportion of established MTCs at hospital level	% of hospitals with established MTCs out of all hospitals (level 4 to 6 hospitals)
Proportion of functional MTCs at hospital level	% of hospitals with functional MTCs out of all hospitals with established MTCs (level 4 to 6 hospitals)
Proportion of facilities with current KEML	% of facilities that have the current KEML out of all facilities
Proportion of health facilities with current clinical guidelines	% of health facilities that have the current clinical guidelines out of all facilities (appropriate to their level)
Proportion of prescriptions complying with guidance in the current KNMF	% of prescriptions complying with guidance in the current KNMF
Proportion of encounters with one or more antibiotics prescribed	% of encounters with one or more antibiotics prescribed at the facility's outpatient department
Proportion of facilities with compliance of at least 60% prescribed antibiotics from the access category	% of health facilities with ≥60% antibiotic prescriptions from the access category in the reporting period
Proportion of medicines prescribed by generic name	% of medicines prescribed by generic name
Average number of medicines per encounter	Total number of medicines prescribed in outpatient department/ number of encounters
Proportion of medicines prescribed from the EML	% of medicines prescribed from those listed in the current KEML
Proportion of prescribed medicines dispensed at the facility	% of prescribed medicines that were dispensed at the facility
Proportion of encounters with an injection prescribed	% of prescriptions with injections in the outpatient department
Proportion of medicines that are adequately labelled	% of medicine packages that are labeled with adequate information to aid rational use by patients
Proportion of tracer essential medicines available in health facilities	Average availability of tracer medicines across health facilities

Monitoring and Evaluation

1. Review and monitoring of utilization of the National Formulary is one of the responsibilities of the NMTC as captured in terms of reference and in its three-year work plan.
2. There are three NMTC subcommittees:
   - » HPT Lists and National Formulary
   - » Clinical guidelines
   - » HPT management and antimicrobial use
3. The frequency of guideline review is every three years.
4. The HPT Strategy 2020-2025 has six strategic pillars, and implementation of a rational HPT use program is under objective 2.8. The indicators in the table above are to be monitored under this objective.
5. The NMTC shall provide support for institutional MTCs to ensure that the KNMF is adapted and implemented at the various levels of use.
6. The NMTC shall endeavour to update the KNMF to align with updated versions of the KEML as well as standard treatment guidelines.

Prescribing Information

Good Prescribing Practice

The process of rational prescribing involves defining the patient's problem; specifying the therapeutic goal; checking effectiveness and safety of available medication; writing the prescription; giving information, including instructions and warnings; and monitoring treatment.

Handwritten prescriptions should be legible. The prescriber should be identifiable and the prescription should be clearly written and signed. Prescriber contact information should be available for ease of communication in case of any clarifications. Prescriber contact should include the clinic or ward where the patient is seen.

- There should be a date of prescription and duration of treatment.
- Prescriptions should be written using international nonproprietary names; internationally accepted abbreviations should be used.
- Decimals should be avoided. As much as possible, strengths of medicines should be written in full to avoid misunderstanding and errors for example, micrograms instead of mcg.

The full name of the patient and age of patient should be clearly indicated. A second patient identifier, for example, the hospital number, should be included to minimize errors. Relevant measurements that guide in dosing, for example, weight and body surface area (BSA), should be included as required.

Repeat prescriptions, especially for chronic conditions, should allow for refill for a period not exceeding three months. Patients on long-term treatment should be reviewed at a health facility at least four times per year to ensure compliance to treatment and monitoring of treatment outcomes.

Prescribing of Narcotics and Psychotropic Substances

Medicines controlled by the Narcotic & Psychotropic Substances Act, formerly CAP 245 (Dangerous Drugs) are required to be written fully **in words, in red font, including the name, dosage strength, frequency of administration, duration of use, and any other requisite information**.

These medicines require a separate prescription written specifically for the items prescribed, in order to be dispensed.

These prescriptions must bear the **full name and signature** of the prescriber.

Dispensing Guidelines

Prior to dispensing a prescription, the law requires the dispensing officer to determine that the prescription complies with all the requirements of a legal prescription.

On receipt of the prescription, the patient's name and age should be verified. A patient profile should be generated, including information on the patient's date of birth, medical conditions, allergies, incapacities, lifestyle factors, and medication and other therapies being received. This information must be obtained with a patient's fully informed consent and is confidential.

The validity of the prescription is established according to the prescribing guidelines and according to suitability, choice of dosage regimen, potential interactions, and adverse reactions.

When there is a potential for therapeutic or brand substitution, the prescriber should be contacted and the rationale for the substitution discussed.

The prescriber should be contacted in the following circumstances:

- If there's doubt about the suitability of the medication for the patient
- If the prescriber's intentions are not clear, if there is a potential for drug misuse
- If there is apparent over- or under-utilisation
- If there is any doubt about the legality of the prescription

If the prescriber is unavailable to accept the pharmacist's or pharmaceutical technologist's advice, the pharmacist or pharmaceutical technologist must make a professional judgement as to the actions required to satisfy the duty of care to the patient. The patient should be offered a full disclosure of the discussions and decisions, so as to understand the outcome.

Health care facilities must keep dispensing records for all medications dispensed.

On dispensing, the items should be selected as the expiry dates are checked. The labels should be clearly written, bearing the patient's name, the medicine's name, and the dosing instructions in an unambiguous manner. The label should be attached to the medicine so as not to hinder verification.

All dispensed medicines should be checked and verified by the dispensing officer. The name, medication, dosage, strength, directions, quantity, written instructions, ancilliary labels, and expiry dates should be checked.

Adequate medicine use counselling should be done, including directions for use and storage of medicines, their actions, precautions, possible adverse effects, and expected outcomes of the medication.

The dispensing officer should confirm that the patient understands their treatment schedule. The patient should be given a chance to ask for clarification of any information given.

Guidelines on Providing Medicine Information to Patients

Patients have a right to participate in making their own medication therapy decisions. In order to do this, they must have enough information about their condition, treatment options, outcomes expected, and the possible results of avoiding treatment. Therefore, the challenge for the dispenser is to make the patient understand the above information so as to make the right informed decision on the treatment option. Discussions should focus on the patient's total medication therapy including:

- Confirmation of the indications for particular medicines, all illnesses or conditions the patient has, and the patient's total medication therapy
- The proposed approach to medicine therapy
- What the proposed treatment entails
- Expected benefits
- Common adverse effects and material risks of treatment
- Whether the treatment is conventional or new
- Other treatment options for the condition
- Certainty of therapeutic outcome
- Consequences of not taking the therapy at all
- Any significant, long-term, non-therapeutic outcome expected, for example, mental, social, sexual impact
- Treatment duration
- Treatment costs involved
- How to use the medicines effectively
- Precautions on using the medicines

Information provided by the dispenser should be in context of the total medication therapy and overall medical and social circumstances.

The dispenser should:

- Offer the patient a quiet confidential setting in which to discuss medication therapy
- Communicate the information in a form that the patient can understand
- Be aware of the information provided by other health care professionals (especially the prescriber)
- Allow the patient enough time to make a decision
- Repeat key information to help the patient understand
- Give well-designed, written medicine information from an authoritative source
- Pay careful attention to the patient's responses to help identify what has or has not been understood

Pharmacovigilance

The Pharmacy and Poisons Board of Kenya has an electronic Pharmacovigilance Reporting System (PVERS) that facilitates reporting of suspected adverse drug reactions, adverse events following immunization, medication errors, and quality issues that affect all HPT. The system can be accessed from https://pv.pharmacyboardkenya.org/

The PVERS platform includes forms for reporting:

1. Suspected Adverse Drug Reactions (yellow form)
2. Poor-Quality Medical Products and Health Technologies (pink form)
3. Adverse Transfusion Reaction (off-white form)
4. Medication Errors (blue form)
5. Medical Devices Incident (green form)
6. Adverse Events Following Immunization (white form)

All information received is in confidence and the details of the reporter always remain anonymous. The information collected is intended to improve patient safety nationally.

Medicine Monographs Section of the Formulary

1. Anaesthetics, Pre- & Intra-Operative Medicines, & Medical Gases

1.1. General Anaesthetics

Anaesthetic drugs may be fatal if inappropriately used. Irrespective of the type of anaesthesia used (i.e., general or regional), it is essential that facilities for intubation, resuscitation, and mechanically assisted ventilation are available.

1.1.1. Inhalational Medicines

Halothane

ATC code: N01AB01

Inhalation, 250-mL bottle, LOU 4

Indications and dose

Adult

Induction of anaesthesia, using a specifically calibrated vaporizer: Gradually increase inspired gas concentration to 2–4%, in oxygen or nitrous oxide–oxygen

Maintenance of anaesthesia (minimum alveolar concentration [MAC] 0.75%, varies with age): 0.5–2%

Paediatric

Induction of anaesthesia: By inhalation through specifically calibrated vaporizer

Infant or **child:** Initially 0.5%, then gradually increase inspired gas concentration to 1.5–2% in oxygen or nitrous oxide–oxygen *Maintenance of anaesthesia: By inhalation through specifically calibrated vaporizer*

Infant or **child:** 0.5–2% in oxygen-air or nitrous oxide–oxygen

Contraindications: History of unexplained jaundice or fever following previous exposure to halothane, family history of malignant hyperthermia, raised cerebrospinal fluid pressure, porphyria

Precautions

» Anaesthetic history should be carefully taken to determine previous exposure and previous reactions to halothane (fulminant hepatic failure is a rare complication of re-exposure to halothane); avoid use if adequate resuscitation facilities are not available.

Hepatic impairment: Avoid if history of unexplained pyrexia or jaundice following previous exposure to halothane.

Adverse effects: Bradycardia, respiratory depression, arrhythmias, hepatitis (may be fatal)

Interactions with other medicines (*indicates serious): Amitriptyline, *chlorpromazine, diazepam, enalapril, epinephrine (adrenaline), *fluphenazine, furosemide, *haloperidol, isoniazid, *levodopa, spironolactone, suxamethonium, vancomycin, vecuronium, *verapamil

Notes

» Does not augment salivary or bronchial secretions

» Cardiac sensitization to the effects of catecholamines

Isoflurane

ATC code: N01AB06

Inhalation, 100% inhalation vapour liquid, 250 mL, LOU 4

Indications and dose

Induction of anaesthesia (in oxygen or nitrous oxide–oxygen) (but indication not recommended in infants and children of all ages): Agent is pungent, hence risk of cough and bronchospasms.

Adult

By inhalation: Initially 0.5%, increased to 3%, adjusted according to response, administered using specifically calibrated vaporizer

Maintenance of anaesthesia (in nitrous oxide–oxygen): By inhalation: 1–2.5%, to be administered using specifically calibrated vaporizer; an additional 0.5–1% may be required when given with oxygen alone or air-oxygen

Maintenance of anaesthesia in caesarean section (in nitrous oxide–oxygen): By inhalation: 0.5–0.75%, to be administered using specifically calibrated vaporizer

Paediatric

Induction of anaesthesia (in oxygen or nitrous oxide–oxygen) (but indication not recommended in infants and children of all ages): Agent is pungent, hence risk of cough and bronchospasm.

Maintenance of anaesthesia (in nitrous oxide–oxygen): By inhalation

Neonate and child: 1–2.5%, to be administered using specifically calibrated vaporizer; an additional 0.5–1% may be required when given with oxygen alone or oxygen –air mixture.

Contraindications: Isoflurane is contraindicated in patients with known sensitivity to isoflurane or to other halogenated anaesthetics and in patients with known or suspected genetic susceptibility to malignant hyperthermia.

Precautions: Children under 2 years - limited experience

Hepatic and renal impairment: No dose adjustments

Pregnancy: May depress neonatal respiration if used during delivery

Breastfeeding: Breastfeeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

Adverse effects: Hypotension, arrhythmias, cardiac arrest, bradycardia and tachycardia, QT prolongation, associated with torsade de pointes, respiratory depression, cough related to induction, malignant hyperthermia, elevated serum creatine kinase,

myoglobinuria, anaphylactic reactions and liver adverse reactions, shivering, hyperkalaemia (perioperative), nausea, vomiting, ileus, agitation, and delirium

Interactions with other medicines

- Beta-sympathomimetic agents like isoprenaline and alpha and beta-sympathomimetic agents like epinephrine and norepinephrine should be used with caution during isoflurane narcosis.
- Non-selective monoamine oxidase inhibitors (MAOIs): Treatment should be stopped 15 days prior to surgery.
- Indirect-acting sympathomimetics (amphetamines and their derivatives, psychostimulants, appetite suppressants, ephedrine, and its derivatives): Treatment should ideally be discontinued several days before surgery.
- Epinephrine by subcutaneous (SC) or gingival injections
- Calcium antagonists, in particular dihydropyridine derivatives
- Beta-blockers
- Medicinal products and compounds that increase the activity of cytochrome P450 (CYP) isoenzyme CYP2E1, such as isoniazid and alcohol
- Isoniazid
- Opioids, benzodiazepines, and other sedative agents
- Concomitant use of succinylcholine
- All commonly used muscle relaxants
- Nitrous oxide

Sevoflurane

ATC code: N01AB08

Inhalation vapour liquid, 250 mL, LOU 5

Indications and dose: Induction of anaesthesia (in oxygen, nitrous oxide–oxygen or oxygen–air)

Adult

By inhalation: Initially 0.5–1%, then increased to up to 8%, increased gradually, according to response, to be administered using specifically calibrated vaporizer.

Maintenance of anaesthesia: In oxygen, nitrous oxide–oxygen, or oxygen–air

By inhalation: 0.5–3%, adjusted according to response, to be administered using specifically calibrated vaporizer

Paediatric

Induction of anaesthesia (in oxygen, nitrous oxide–oxygen, or air–oxygen)

By inhalation

Neonate: Up to 4%, adjusted according to response, to be administered using specifically calibrated vaporiser.

Child: Initially 0.5–1%, then increase to up to 8%, increased gradually, according to response, to be administered using specifically calibrated vaporiser

Maintenance of anaesthesia: In oxygen, nitrous oxide–oxygen, or air–oxygen

By inhalation

Neonate: 0.5–2%, adjusted according to response, to be administered using specifically calibrated vaporizer

Child: 0.5–3%, adjusted according to response, to be administered using specifically calibrated vaporizer

Contraindications

- Patients with known or suspected sensitivity to sevoflurane or other halogenated anaesthetics (e.g., history of liver function disorder, fever, or leucocytosis of unknown cause after anaesthesia with one of these agents)
- Patients with known or suspected genetic susceptibility to malignant hyperthermia
- Patients in whom general anaesthesia is contraindicated

Precautions

- Susceptibility to QT-interval prolongation
- Sevoflurane may cause respiratory depression, which may be augmented by narcotic premedication or other agents causing respiratory depression. Respiration should be supervised and if necessary, assisted.
- Should be administered only by persons trained in the administration of general anaesthesia; facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available.
- **The concentration of sevoflurane being delivered from a vaporizer must be known exactly.** As volatile anaesthetics differ in their physical properties, only vaporizers specifically calibrated for sevoflurane must be used.
- Administration of general anaesthesia must be individualized based on the patient's response. Hypotension and respiratory depression increase as anaesthesia is deepened.

Hepatic and renal impairment: Use with caution

Pregnancy: May depress neonatal respiration if used during delivery

Breastfeeding: Can be resumed as soon as mother has recovered sufficiently from anaesthesia

Adverse effects: Drowsiness, fever, hypothermia, asthma, atrioventricular block, confusion, dystonia, intracranial pressure increased, muscle rigidity, nephritis tubulointerstitial, oedema, pancreatitis

Interactions with other medicines:

- Beta-sympathomimetic agents like isoprenaline and alpha- and beta-sympathomimetic agents like epinephrine and norepinephrine
- Non-selective MAOIs

» Calcium antagonists, in particular dihydropyridine derivates

» Succinylcholine

1.1.2. Injectable medicines (intravenous anaesthetic agents and sedatives)

Dexmedetomidine

ATC code: N05CM18

Injection, 100 micrograms/mL (2 mL), LOU 5

Indications and dose: Maintenance of sedation during intensive care

Adult

By IV infusion: 0.7 microgram/kg/hour, adjusted according to response, usual dose 0.2–1.4 micrograms/kg/hour

Paediatric

By IV infusion: 0.2–0.7 micrograms/kg/hour

Contraindications: Pregnancy, breastfeeding, hepatic impairment, acute cerebrovascular disorders, second- or third-degree Atrioventricular (AV) block (unless pacemaker fitted), uncontrolled hypotension

Precautions

» Should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management

» Abrupt withdrawal after prolonged use; bradycardia, heart block, elderly (risk of hypotension), ischaemic heart disease (especially at higher doses), malignant hyperthermia, severe cerebrovascular disease (especially at higher doses), severe neurological disorders, spinal cord injury

» **Hepatic impairment:** Use with caution (increased risk of toxicity due to decreased clearance); consider dose reduction

» **Renal impairment:** No dose adjustment is required

» **Pregnancy**: Avoid unless potential benefit outweighs risk—toxicity in animal studies

» **Breastfeeding:** Avoid unless potential benefit outweighs risk—present in milk in animal studies

Adverse effects: Agitation, arrhythmias, dry mouth, hyperglycaemia hypertension, hyperthermia, hypoglycaemia, hypotension, myocardial infarction (MI), myocardial ischaemia, nausea, respiratory depression, vomiting, abdominal distension, apnoea, atrioventricular block, dyspnoea, hallucination, hypoalbuminaemia, metabolic acidosis, thirst

Interaction with other medicines: Anaesthetics, sedatives, hypnotics, opioids, isoflurane, propofol, alfentanil, midazolam, substrates with dominant CYP2B6 metabolism, beta-blockers

Notes

» Directions of administration: Dilute before use; for IV infusion, give continuously in glucose 5% or sodium chloride 0.9%, dilute to a concentration of 4 micrograms/mL.

» Errors have occurred because of misinterpretation of dosing information; maintenance dose expressed as micrograms/kg/hour

Etomidate

ATC code: N01AX07

Injection, 2mg/mL (10 mL Vial), LOU 6

Indications and dose

Adult

For induction of general anesthesia, intravenous: 0.3 mg/kg, injected over a period of 30 to 60 seconds but can range from 0.2 mg/kg to 0.6 mg/kg of body weight, individualized in each case.

Paediatric

<15 years: same dosage as adults. A supplementary dose of up to 30% of the normal dose for adults is sometimes necessary to obtain the same depth and duration of sleep as obtained in adults

Contraindications: Hypersensitivity to etomidate or any of the excipients

Precautions: Reduce dose in patients with liver cirrhosis, or in those who have already received neuroleptic, opiate or sedative agents, Induction with etomidate may be accompanied by a slight and transient drop in blood pressure due to a reduction of the peripheral vascular resistance, respiratory depression and the possibility of apnoea need to be managed with use of etomidate, Single induction doses of etomidate can lead to transient adrenal insufficiency and decreased serum cortisol levels, should be used with caution in critically ill patients, including patients with sepsis, should be used with caution in elderly patients, since the potential exists for decreases in cardiac output, should be administered slowly, exacerbation of underlying myocardial dysfunction especially in hypertensive patients.

Hepatic & renal impairment: Risk of toxicity may increase in patients with renal and hepatic impairment. Individualize the dose as required as you monitor the hepatic and renal functions.

Use in pregnancy: should be used during pregnancy only if the potential benefit justifies the risks to the fetus.

Breastfeeding: Breast-feeding should be discontinued during treatment and for a period of approximately 24 hours after treatment with entomidate.

Adverse effects: transient venous pain on injection, transient skeletal muscle movements, opsoclonus and adrenal suppression, hiccups, Apnea (duration: 5-90 seconds), Arrhythmias,

Hyperventilation, Hypertension, Hypotension, Hypoventilation, Laryngospasm, Nausea/vomiting, Oxygen desaturation, Snoring

Interactions with other medicines (*indicates serious): hypnotic effect of etomidate may be enhanced by neuroleptic drugs, opioids, sedatives and alcohol, induction with etomidate may be accompanied by a slight and transient reduction in peripheral resistance which may enhance the effect of other drugs reducing blood pressure**,** etomidate increases levels of Adrenaline, noradrenaline, and Phenylephrine by decreasing metabolism, doxapram**,** *benzhydrocodone/paracetamol, *calcium/magnesium/potassium/sodium oxybates, *fentanyl, *fentanyl intranasal, *fentanyl transmucosal, *hydrocodone, *metoclopramide intranasal, *olopatadine intranasal.

Notes: Elderly patients require lower doses (0.15mg to 0.2mg) of etomidate than younger patients, consider lidocaine pre-administration to minimize injection-site pain

Fentanyl

ATC code, N01AH01

Injection (as citrate), 50 micrograms/mL (2-mL amp), LOU 4

Indications and dose

Adults and children aged 12 years and above:

General Anesthesia

Minor surgery: 0.5-2 mcg/kg/dose IV

Major surgery: 2-20 mcg/kg/dose initially; 1-2 mcg/kg/hr maintenance infusion IV; discontinue infusion 30-60 min prior to end of surgery; limit total fentanyl doses to 10-15 mcg/kg for fast tracking and early extubation

Surgery Premedication:

50-100 mcg/dose IM or slow IV 30-60 min prior to surgery

Adjunct to regional anesthesia: 25-100 mcg/dose slow IV over 1-2 min

Paediatric

Induction of anaesthesia Child 2-12years: 2-3mcg/kg

Maintenance of anaesthesia: Child 2-12years 2-3mcg/kg

Contraindications: Hypersensitivity to the active substance or to any of the excipients, known intolerance to fentanyl or other morphino-mimetics, respiratory depression without mechanical ventilation, obstructive airway disease, patients with post-operative interventions in the biliary tract, concurrent use with monoamine oxidase inhibitors or within 2 weeks of discontinuation.

Precautions: Repeated intraoperative doses should be given with care because the resulting respiratory depression can persist post-operatively.

Pregnancy: Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate, Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breastfeeding: The risk/benefit of breast-feeding following fentanyl administration should be considered.

Adverse effects: respiratory depression, apnea, muscle rigidity, bradycardia, Hypertension, hypotension, visual disturbances, agitation, sedation, venous pain, arrhythmia, tachycardia, pruritus, nausea and vomiting, emesis

Interaction with other medicines: Barbiturates, benzodiazepines, neuroleptics, other non-selective CNS depressants (e.g., alcohol), beta-blockers, suxamethonium, halothane, vecuronium, IV midazolam

Ketamine

ATC code: N01AX03

Injection, 50 mg (as HCl)/mL in 10-mL vial, LOU 4

Indications and dose

- Induction and maintenance of anaesthesia, analgesia for painful procedures of short duration
- Titrate dose to effect; give the IV injection over at least 60 seconds

Adult

Induction and maintenance of anaesthesia for short procedures

By IM injection: Initially 4–6 mg/kg, adjusted according to response

By IV injection: Initially 1–2 mg/kg, adjusted according to response, administered over at least 60 seconds, a dose of 2 mg/kg usually produces 5–10 minutes of surgical anaesthesia

Diagnostic manoeuvres and procedures not involving intense pain

By IM injection: Initially 4 mg/kg induction and maintenance of anaesthesia for long procedures

By IV infusion: Initially 0.5–2 mg/kg, using an infusion solution containing 1 mg/mL, maintenance 10–45 micrograms/kg/min (0.01–0.045 mg/kg/min), adjusted according to response

Paediatric

Neonate, infant, or **child:** 1–2 mg/kg produces 5–10 minutes of surgical anaesthesia, adjusted according to response

IM injection

Neonate: 4 mg/kg for 15 minutes of surgical anaesthesia (adjusted according to response)

Infant or **child:** 4–6 mg/kg (4 mg/kg sufficient for some diagnostic procedures), adjusted according to response

Induction and maintenance of anaesthesia (longer procedures)

Continuous IV infusion

Neonate: Initially 0.5–2 mg/kg followed by a continuous IV infusion of 500 micrograms/kg/hour adjusted according to response, up to 2 mg/kg/hour may be used to produce deep anaesthesia

Infant or **child:** Initially 0.5–2 mg/kg followed by a continuous IV infusion of 0.6–2.7 mg/kg/hour adjusted according to response.

Contraindications: Thyrotoxicosis, hypertension, severe cardiac disease, history of cerebrovascular accident, cerebral trauma, intracerebral mass or haemorrhage or other cause of raised intracranial pressure, eye injury and increased intraocular pressure, psychiatric disorders, particularly hallucinations, porphyria

Precautions

- Increased cerebrospinal fluid pressure
- Predisposition to hallucinations or nightmares
- Supplementary analgesia often required in surgical procedures involving visceral pain pathways (morphine may be used but addition of nitrous oxide will often suffice)
- Administer an antisialagogue to prevent excessive salivation leading to respiratory difficulties
- During recovery, patient must remain undisturbed but under observation
- Skilled tasks: Warn patient or caregiver about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike or operating machinery, for 24 hours

Adverse effects: Raised blood pressure and pulse rate; raised intracranial pressure; raised intraocular pressure; hypersalivation; increased muscle tone; emergence reactions, including hallucinations, restlessness, confusion, and irrational behavior; hypotension; bradycardia; arrhythmias

Interactions with other medicines (*indicates serious): Amitriptyline, *chlorpromazine, diazepam, enalapril, *fluphenazine, furosemide, *haloperidol, isoniazid, spironolactone, vancomycin, *verapamil

Notes

- For continuous IV infusion, dilute to a concentration of 1 mg/mL with glucose 5% or sodium chloride 0.9%, use microdrip infusion for maintenance of anaesthesia.
- Premedication with an anticholinergic to reduce secretions is recommended before its use in anaesthesia.
- Anaesthesia persists for up to 15 minutes after a single IV injection and is characterized by profound analgesia.
- Subanaesthetic doses may be used to provide analgesia and sedation for painful procedures of short duration (e.g., dressing burns, radiotherapeutic procedures, marrow sampling, and minor orthopaedic procedures).
- Recovery is relatively slow and associated with a high incidence of hallucinations and other emergence reactions, such as delirium.

Midazolam

ATC code: N05CD08

Injection, 1 mg as HCl/mL in 5-mL amp, LOU 4

Indications and dose

Adult

Conscious sedation for procedures, by slow IV injection: Initially 2–2.5 mg, to be administered 5–10 minutes before procedure at a rate of approximately 2 mg/min, increased in steps of 1 mg if required, usual total dose is 3.5–5 mg, maximum 7.5 mg per course

- Elderly: Initially 0.5–1 mg, to be administered 5–10 minutes before procedure at a rate of approximately 2 mg/min, increased in steps of 0.5–1 mg if required, maximum 3.5 mg per course.

Sedative in combined anaesthesia, initially by IV injection: 30–100 micrograms/kg (0.03–0.1 mg)/kg), repeated, if necessary, alternatively (by continuous IV infusion) 30–100 micrograms/kg/hour

- Elderly: Lower doses needed

Premedication by deep IM injection: 70–100 micrograms/kg, to be administered 20–60 minutes before induction; for debilitated patients, use elderly dose

- Elderly: 25–50 micrograms/kg, to be administered 20–60 minutes before induction

Premedication by IV injection: 1–2 mg, repeated, if necessary, to be administered 5–30 minutes before procedure; for debilitated patients, use elderly dose

- Elderly: 0.5 mg, repeated, if necessary, initial dose to be administered 5–30 minutes before procedure, repeat dose slowly as required

Induction of anaesthesia, by slow IV injection: 150–200 micrograms/kg (0.15 mg to 0.2 mg/kg) daily in divided doses (max. per dose 5 mg), dose to be given at intervals of 2 minutes, maximum total dose 600 micrograms/kg; for debilitated patients, use elderly dose

- Elderly: 50–150 micrograms/kg daily in divided doses (max. per dose 5 mg), dose to be given at intervals of 2 minutes, maximum total dose 600 micrograms/kg

Sedation of patient receiving intensive care, initially by slow IV injection: Initially 30–300 micrograms/kg, dose to be given in steps of 1–2.5 mg every 2 minutes, then (by slow IV injection or by continuous IV infusion) 30–200 micrograms/kg/hour, reduce dose (or reduce or omit initial dose) in hypovolaemia, vasoconstriction, or hypothermia; lower doses may be adequate if opioid analgesic also used

Paediatric

Conscious sedation for procedures

Oral

Child: 500 micrograms/kg (max. per dose 20 mg), to be administered 30–60 minutes before procedure

Buccal administration

Child 6 months–9 years: 200–300 micrograms/kg (max. per dose 5 mg)

Child 10–17 years (body weight up to 70 kg): 6–7 mg

Child 10–17 years (body weight 70 kg and above): 6–7 mg (max. per dose 8 mg)

By rectum

Child 6 months–11 years: 300–500 micrograms/kg, to be administered 15–30 minutes before procedure

By IV injection

Child 1 month–5 years: Initially 25–50 micrograms/kg, to be administered over 2–3 minutes, 5–10 minutes before procedure; dose can be increased, if necessary, in small steps to maximum total dose per course, maximum 6 mg per course

Child 6–11 years: Initially 25–50 micrograms/kg, to be administered over 2–3 minutes, 5–10 minutes before procedure; dose can be increased, if necessary, in small steps to maximum total dose per course, maximum 10 mg per course

Child 12–17 years: Initially 25–50 micrograms/kg, to be administered over 2–3 minutes, 5–10 minutes before procedure; dose can be increased, if necessary, in small steps to maximum total dose per course, maximum 7.5 mg per course

Premedication

Oral

Child: 500 micrograms/kg (max. per dose 20 mg), to be taken 15–30 minutes before the procedure

By rectum

Child 6 months–11 years: 300–500 micrograms/kg, to be administered 15–30 minutes before induction

Induction of anaesthesia (rarely used)

By slow IV injection

Child 7–17 years: Initially 150 micrograms/kg (max. per dose 7.5 mg), dose to be given in steps of 50 micrograms/kg (max. 2.5 mg) over 2–5 minutes, wait for 2–5 minutes before subsequent dosing, then 50 micrograms/kg every 2 minutes (max. per dose 2.5 mg) if required, maximum 500 micrograms/kg per course, maximum 25 mg per course

Sedation of patient receiving intensive care

Initially by slow IV injection

Child 6 months–11 years: Initially 50–200 micrograms/kg, to be administered over at least 3 minutes, followed by (by continuous IV infusion) 30–120 micrograms/kg/hour, adjusted according to response; initial dose may not be required and lower maintenance doses needed if opioid analgesics also used; reduce dose (or reduce or omit initial dose) in hypovolaemia, vasoconstriction, or hypothermia

Child 12–17 years: Initially 30–300 micrograms/kg, dose to be given in steps of 1–2.5 mg every 2 minutes, followed by (by continuous IV infusion) 30–200 micrograms/kg/hour, adjusted according to response; initial dose may not be required and lower maintenance doses needed if opioid analgesics also used; reduce dose (or reduce or omit initial dose) in hypovolaemia, vasoconstriction, or hypothermia

By continuous IV infusion

Neonate up to 32 weeks corrected gestational age: 60 micrograms/kg/hour for 24 hours, then reduced to 30 micrograms/kg/hour, adjusted according to response for maximum treatment duration of 4 days

Neonate 32 weeks corrected gestational age and above: 60 micrograms/kg/hour, adjusted according to response for maximum treatment duration of 4 days

Child 1–5 months: 60 micrograms/kg/hour, adjusted according to response. **Contraindications:** Injection, oral: Hypersensitivity to midazolam or any component of the formulation, intrathecal or epidural injection of parenteral forms containing preservatives (i.e., benzyl alcohol), use in premature infants for parenteral forms containing benzyl alcohol, acute narrow-angle glaucoma

Precautions:

- May cause central nervous system (CNS) depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (e.g., operating machinery, driving)
- Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines; risk may be increased in adolescent/paediatric patients, geriatric patients, or patients with a history of alcohol use disorder or psychiatric/personality disorders (Mancuso 2004)
- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia
- Cardiorespiratory effects: Injection, oral: Has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings, airway obstruction, desaturation, hypoxia, and apnea have also been reported, most often when used concomitantly with other CNS depressants (e.g., opioids)

Hepatic impairment: Single dose: No dosage adjustment recommended; patients with hepatic impairment may be more sensitive compared to patients without hepatic impairment, anticipate longer duration of action

Renal impairment: Use with caution in patients with renal impairment; half-life of midazolam and metabolites may be prolonged

Multiple dosing or continuous infusion: Expect longer duration of action and accumulation, based on patient response, dosage reduction likely to be necessary

Breastfeeding: Avoid for 24 hours after administration

Adverse effects: Vomiting, apnea, bradypnea, decreased tidal volume, bradycardia, hypotension, syncope

Interaction with other medicines: Concurrent use of oral midazolam with protease inhibitors (atazanavir, atazanavir-cobicistat, darunavir, indinavir, lopinavir-ritonavir, nelfinavir, ritonavir, saquinavir, tipranavir), concurrent use of oral or injectable midazolam with fosamprenavir; prolonged sedation, close monitoring required

Notes

- Midazolam should be used only in hospital or ambulatory care settings, including physicians' and dentists' offices, that can provide continuous monitoring of respiratory and cardiac function.
- Concomitant use of benzodiazepines and opioids may result in profound sedation and respiratory depression.
- IV infusion should be given continuously in glucose 5% or sodium chloride 0.9%.
- For administration by mouth for sedation and premedication; injection solution may be diluted with apple or black currant juice, chocolate sauce, or cola.

Propofol

ATC code: N01AX10

Injection,10 mg/mL in 20-mL vial, LOU 4

Indications and dose

Adult

Induction of anaesthesia using 0.5%or 1% injection

By slow IV injection or by IV

18–54 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response; for debilitated patients use dose for 55 years and over

55 years and over: Usual dose 1–1.5 mg/kg, to be administered at a rate of 20 mg every 10 seconds until response

Induction of anaesthesia using 2% injection

By IV infusion

18–54 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response; for debilitated patients use dose for 55 years and over

55 years and over: Usual dose 1–1.5 mg/kg, to be administered at a rate of 20 mg every 10 seconds until response

Maintenance of anaesthesia using 1% injection

INITIALLY by IV infusion: Usual dose 4–12 mg/kg/hour, alternatively (by slow IV injection) 25–50 mg, dose may be repeated according to response; for debilitated patients use dose for elderly

- **Elderly:** Usual dose 3–6 mg/kg/hour, alternatively (by slow IV injection) 25–50 mg; dose may be repeated according to response

Maintenance of anaesthesia using 2% injection, by IV infusion: Usual dose 4–12 mg/kg/hour, for debilitated patients use dose for elderly

- **Elderly:** Usual dose 3–6 mg/kg/hour

Sedation of ventilated patients in intensive care using 1% or 2% injection by continuous IV infusion: Usual dose 0.3–4 mg/kg/hour, adjusted according to response

Induction of sedation for surgical and diagnostic procedures using 0.5%or 1% injection by slow IV injection: Initially 0.5–1 mg/kg, to be administered over 1–5 minutes; dose and rate of administration adjusted according to desired level of sedation and response

Maintenance of sedation for surgical and diagnostic procedures using 0.5% injection by IV infusion: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow IV injection) 10–20 mg (if rapid increase in sedation required); patients over 55 years or debilitated may require lower initial dose and rate of administration

Maintenance of sedation for surgical and diagnostic procedures using 1% injection by IV infusion: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow IV injection) 10–20 mg (if rapid increase in sedation required); patients over 55 years or debilitated may require lower initial dose and rate of administration

Maintenance of sedation for surgical and diagnostic procedures using 2% injection by *IV infusion:* Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow IV injection) 10–20 mg, using 0.5% or 1% injection (if rapid increase in sedation required); patients over 55 years or debilitated may require lower initial dose and rate of administration

Paediatric

Induction of anaesthesia using 0.5% or 1% injection by slow IV injection or by IV infusion

Child 1 month–16 years: Usual dose 2.5–4 mg/kg, dose adjusted according to age, body weight, and response

Child 17 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response

Induction of anaesthesia using 2% injection by IV infusion

Child 3–16 years: Usual dose 2.5–4 mg/kg, dose adjusted according to age, body weight, and response

Child 17 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response

Maintenance of anaesthesia using 1% injection by continuous IV infusion

Child 1 month–16 years: Usual dose 9–15 mg/kg/hour, dose adjusted according to age, body weight, and response

Child 17 years: Usual dose 4–12 mg/kg/hour, adjusted according to response

Maintenance of anaesthesia using 2% injection *by continuous IV infusion*

Child 3–16 years: Usual dose 9–15 mg/kg/hour, dose adjusted according to age, body weight, and response

Child 17 years: Usual dose 4–12 mg/kg/hour, adjusted according to response

Sedation of ventilated patients in intensive care using 1% or 2% injection by continuous IV infusion

Child 16–17 years: Usual dose 0.3–4 mg/kg/hour, adjusted according to response

Induction of sedation for surgical and diagnostic procedures using 0.5% or 1% injection by slow IV injection

Child 1 month–16 years: Initially 1–2 mg/kg, dose, and rate of administration adjusted according to desired level of sedation and response

Child 17 years: Initially 0.5–1 mg/kg, to be administered over 1–5 minutes; dose and rate of administration adjusted according to desired level of sedation and response

Maintenance of sedation for surgical and diagnostic procedures using 0.5% injection by IV infusion

Child 17 years: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow IV injection) 10–20 mg (if rapid increase in sedation required)

Maintenance of sedation for surgical and diagnostic procedures using 1%injection by IV infusion

Child 1 month–16 years: Usual dose 1.5–9 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow IV injection) up to 1 mg/kg (if rapid increase in sedation required)

Child 17 years: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow IV injection) 10–20 mg (if rapid increase in sedation required)

Maintenance of sedation for surgical and diagnostic procedures using 2% injection by IV infusion

Child 3–16 years: Usual dose 1.5–9 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response

Child 17 years: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow IV injection) 10–20 mg, using 0.5% or 1% injection (if rapid increase in sedation required)

Contraindications

- Children under 16 years receiving intensive care
- Use in intensive care associated with risk of propofol infusion syndrome (potentially fatal effects, including metabolic acidosis, arrhythmias, cardiac failure, rhabdomyolysis, hyperlipidaemia, hyperkalaemia, hepatomegaly, and renal failure)

Precautions

- Propofol should only be administered by or under the direct supervision of personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.
- Acute circulatory failure (shock), cardiac impairment, cardiovascular disease, epilepsy, fixed cardiac output, hypotension, hypovolaemia, raised intracranial pressure, respiratory impairment

Hepatic and renal impairment: Use with caution.

Pregnancy: May depress neonatal respiration if used during delivery

Breastfeeding: Can be resumed as soon as mother has recovered sufficiently from anaesthesia

Adverse effects: Apnoea arrhythmias, headache, hypotension, localized pain, nausea, vomiting, thrombosis, epileptiform seizure (may be delayed), pancreatitis, post-procedural complications, pulmonary oedema, sexual disinhibition, soft tissue necrosis, urine discoloration, drug-use disorders, dyskinesia, euphoric mood, heart failure, hepatomegaly, hyperkalaemia, hyperlipidaemia, metabolic acidosisrenal failure, respiratory depression, rhabdomyolysis, bradycardia, pain on injection, propofol infusion syndrome, including metabolic acidosis, arrhythmias, cardiac failure, rhabdomyolysis, hyperlipidaemia, hyperkalaemia, hepatomegaly, and renal failure

Interactions with other medicines (*indicates serious): Rifampicin, benzodiazepines, parasympatholytic agents or volatile anaesthetics, valproate, opioids, suxamethonium, neostigmine, alcohol, ciclosporin

Notes

- Monitoring requirements: Monitor blood lipid concentration if risk of fat overload or if sedation longer than 3 days
- **Directions for administration:** Shake before use, microbiological filter not recommended, may be administered via a Y-piece close to injection site co-administered with glucose 5% or sodium chloride 0.9%
- 1% emulsion for injection or infusion, may be administered undiluted or diluted with glucose 5%

Remifentanyl

ATC code: N01AH06

Powder for injection, 2 mg/2 mL, LOU 5

Indications and dose

Adult

Analgesia and enhancement of anaesthesia at induction: (initial bolus injection) by IV injection: Initially 0.25–1 microgram/kg, dose to be administered over at least 30 seconds, if patient is to be intubated more than 8 minutes after start of IV infusion, initial bolus IV injection dose is not necessary

Analgesia and enhancement of anaesthesia at induction with or without initial bolus dose by IV infusion: 30–60 micrograms/kg/hour, if patient is to be intubated more than 8 minutes after start of IV infusion, initial bolus IV injection dose is not necessary

Assisted ventilation: Analgesia and enhancement of anaesthesia during maintenance of anaesthesia (initial bolus injection) by IV injection: Initially

0.25–1 microgram/kg, dose to be administered over at least 30 seconds

Assisted ventilation: Analgesia and enhancement of anaesthesia during maintenance of anaesthesia with or without initial bolus dose by IV infusion: 3–120 micrograms/kg/hour, dose to be administered according to anaesthetic technique and adjusted according to response, in light anaesthesia additional doses can be given by IV injection every 2–5 minutes during IV infusion

Spontaneous respiration: Analgesia and enhancement of anaesthesia during maintenance of anaesthesia by IV infusion: Initially 2.4 micrograms/kg/hour, adjusted according to response, usual dose 1.5–6 micrograms/kg/hour

Assisted ventilation: Analgesia and sedation in intensive care patients (for max 3 days) by IV infusion: Initially 6–9 micrograms/kg/hour, then adjusted in steps of 1.5 micrograms/kg/hour, allow at least 5 minutes between dose adjustments, usual dose 0.36–44.4 micrograms/kg/hour, if an infusion rate of 12 micrograms/kg/hour does not produce adequate sedation add another sedative

Assisted ventilation: additional analgesia during stimulating or painful procedures in intensive-care patients by IV infusion: Usual dose 15–45 micrograms/kg/hour, maintain infusion rate of at least 6 micrograms/kg/hour for at least 5 minutes before procedure and adjust every 2–5 minutes according to requirements

Paediatric

Analgesia and enhancement of anaesthesia at induction: Initial bolus injection by IV injection

Child 12–17 years: Initially 0.25–1 microgram/kg, dose to be administered over at least 30 seconds, if child is to be intubated more than 8 minutes after start of IV infusion, initial bolus IV injection dose is not necessary

Analgesia and enhancement of anaesthesia at induction with or without initial bolus dose by IV infusion

Child 12–17 years: 30–60 micrograms/kg/hour, if child is to be intubated more than 8 minutes after start of IV infusion, initial bolus IV injection dose is not necessary

Assisted ventilation: Analgesia and enhancement of anaesthesia during maintenance of anaesthesia (initial bolus injection) by IV injection

Child 1 month–11 years: Initially 0.1–1 microgram/kg, dose to be administered over at least 30 seconds (omitted if not required)

Child 12–17 years: Initially 0.1–1 microgram/kg, dose to be administered over at least 30 seconds (omitted if not required)

Assisted ventilation: Analgesia and enhancement of anaesthesia during maintenance of anaesthesia with or without initial bolus dose by IV infusion

Neonate: 24–60 micrograms/kg/hour, additional doses of 1 microgram/kg can be given by IV injection during the IV infusion

Child 1 month–11 years: 3–78 micrograms/kg/hour, dose to be administered according to anaesthetic technique and adjusted according to response; additional doses can be given by IV injection during the IV infusion

Child 12–17 years: 3–120 micrograms/kg/hour, dose to be administered according to anaesthetic technique and adjusted according to response; additional doses can be given by IV injection during the IV infusion

Spontaneous respiration: Analgesia and enhancement of anaesthesia during maintenance of anaesthesia by IV infusion

Child 12–17 years: Initially 2.4 micrograms/kg/hour, adjusted according to response, usual dose 1.5–6 micrograms/kg/hour

Contraindications

- Analgesia in conscious patients
- As glycine is present in the formulation, remifentanil is contraindicated for epidural and intrathecal use.
- Hypersensitivity to remifentanil and other fentanyl analogues or any other component of remifentanil
- Remifentanil is contraindicated for use as the sole agent for induction of anaesthesia.

Hepatic impairment: Caution in severe impairment

Renal impairment: No dose adjustment necessary in renal impairment

Pregnancy: No information available

Breastfeeding: Avoid for 24 hours after administration - present in milk in animal studies

Adverse effects: Apnoea, muscle rigidity, post-procedural complications, hypoxia, cardiac arrest

Interactions with other medicines

- Inhaled and IV anaesthetics and benzodiazepines
- Cardiac depressant drugs, such as beta-blockers and calcium channel-blocking (CCB) agents

Notes

- Doses at extremes of body weight: To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body weight.
- Should not be given by IV bolus injection intra-operatively, but it is well suited to continuous infusion; a supplementary analgesic is given before stopping infusion of remifentanil.

Directions for administration:

- **Child 1–12 years:** for IV injection, reconstitute to a concentration of 1 mg/mL; for continuous IV infusion, dilute further with glucose 5% or

sodium chloride 0.9% to a concentration of 20–25 micrograms/mL

» **Child 12–18 years:** for IV injection, reconstitute to a concentration of 1 mg/mL; for continuous IV infusion, dilute further with glucose 5% or sodium chloride 0.9% to a concentration of 20–250 micrograms/mL (usually 50 micrograms/mL)

Thiopental Sodium

ATC code: N01AF03

Powder for injection, 500 mg (sodium salt) in vial, LOU 4

Indications and dose

Adult

Induction of anaesthesia prior to administration of inhalational anaesthetic, anaesthesia of short duration by IV injection: Usually as a 2.5% (25 mg/mL) solution over 10–15 seconds, 100–150 mg (reduced in elderly or debilitated patients), followed by a further 100–150 mg if necessary, according to response after 30–60 seconds, or up to 4 mg/kg (maximum 500 mg)

Paediatric

Induction of anaesthesia, anaesthesia of short duration (<15–20 minutes), slow IV injection: usually as a 2.5% (25 mg/mL) solution over 10–15 seconds:

Neonate: Initially up to 2 mg/kg, then 1 mg/kg repeated as necessary (maximum total dose 4 mg/kg)

Infant or **child:** Initially up to 5 mg/kg, then 1 mg/kg repeated as necessary (maximum total dose 7 mg/kg)

Contraindications: Inability to maintain airway, hypersensitivity to barbiturates, severe cardiovascular disease, dyspnoea or obstructive respiratory disease, porphyria

Precautions

» Asthma, hypotension, cardiovascular disease, myotonic dystrophy

» Reconstituted solution is highly alkaline: extravasation can result in extensive tissue necrosis and sloughing

» Intraarterial injection causes intense pain and may result in arteriospasm,

» Rapid administration may result in severe hypotension and hiccups, renal impairment, hepatic impairment.

» Skilled tasks: Warn patient or caregiver about risks of undertaking tasks requiring attention or coordination, for example, riding a bike or operating machinery, for 24 hours.

Hepatic impairment: Reduce dose for induction in severe liver disease.

Renal impairment: May need to reduce dose in severe impairment, administer slowly

Adverse effects: Hypotension, transient erythema, injection site reactions, cardiorespiratory depression, myocardial depression, prolonged somnolence and recovery, cough, sneezing, cardiac arrhythmias, laryngospasm, rash, allergic reactions, anaphylaxis, bronchospasm, haemolytic anaemia

Interactions with other medicines (*indicates serious): Amitriptyline, *chlorpromazine, diazepam, enalapril, *fluphenazine, furosemide, *haloperidol, isoniazid, silver sulfadiazine, spironolactone, sulfadiazine, sulfadoxine + pyrimethamine, sulfamethoxazole + trimethoprim, vancomycin, *verapamil

Notes

» For IV injection, should be diluted to a concentration of 25 mg/mL with water for injection, given over at least 10–15 seconds.

» Rapid IV injection should be avoided (may cause hypotension or decreased cardiac output).

» Thiopental does not have analgesic properties.

» Monitoring for hypotension and respiratory compromise is required.

» Lower doses are needed in shock and low cardiac output states.

» Repeated doses have a cumulative effect, especially in neonates where recovery is slower.

» Reconstitution: Solutions containing 25 mg/mL should be freshly prepared by mixing 20 mL of water for injection with the contents of a 0.5 g vial. Discard any solution more than 24 hours old; discard any solution that is cloudy, precipitated, or crystallized.

1.2. Local Anaesthetics

For spinal, epidural, caudal or IV regional anaesthesia, use **preservative-free** injections.

Drugs used for conduction anaesthesia (also termed local or regional anaesthesia) reversibly block conduction along nerve fibres. Local anaesthetics have variable properties and a range of uses. These include topical (surface) anaesthesia, local anaesthesia, and more specialized anaesthetic procedures requiring higher level technical skills (e.g., nerve blocks and regional, epidural, and spinal anaesthesia).

Local anaesthetic toxicity

» Local anaesthetic systemic toxicity is usually due to excessively high plasma concentrations.

» Therefore, great care should be taken to avoid accidental intravascular injection or unwanted systemic absorption. Intralipid should be available for management of local anaesthetic systemic toxicity (refer to intralipid section–lipid emulsion monograph).

» Facilities for resuscitation should be available at all times.

Bupivacaine

ATC code: N01BB01 and N01BB51

Injection, 0.5% (HCl) in 10-mL vial, LOU 4

Injection for spinal anaesthesia, 0.5% (HCl) in 5 mg/mL with 8% glucose solution (80 mg/mL) 4-mL amp, LOU 4

Indications and dose

Adult

Local infiltration, peripheral nerve block, epidural block,

sympathetic block by regional administration: 75–150 mg, dose administered using a 5 mg/mL (0.5%) solution

Surgical anaesthesia, field block by regional administration: Up to 150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

Surgical anaesthesia, thoracic epidural block by thoracic epidural: 12.5–50 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

Surgical anaesthesia, caudal epidural block by regional administration: 50–150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

Surgical anaesthesia, major nerve block by regional administration: 50–175 mg, dose administered using 5 mg/mL (0.5%) solution

Acute pain, intra-articular block by intra-articular injection: Up to 100 mg, dose administered using a 2.5 mg/mL (0.25%) solution; *when co-administered with bupivacaine by another route:* Total max. 150 mg

Acute pain, thoracic epidural block by continuous epidural infusion: 6.3–18.8 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution, maximum 400 mg per day

Acute pain, labour by continuous epidural infusion: 6.25–12.5 mg/hour, dose administered using a 1.25 mg/mL (0.125%) solution; maximum 400 mg per day

Acute pain, lumbar epidural block

By lumbar epidural: Initially 15–37.5 mg, then (by lumbar epidural) 15–37.5 mg, repeated as required at intermittent injection using a 2.5 mg/mL (0.25%) solution; *alternatively, by continuous epidural infusion*: 12.5–18.8 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution, maximum 400 mg per day

Acute pain, field block by regional administration: Up to 150 mg, dose administered using a 2.5 mg/mL (0.25%) solution

Paediatric

- Dose needs to be adjusted according to child's physical status and nature of procedure.
- Do not use solutions containing preservatives for spinal, epidural or caudal anaesthesia.

Local infiltration: 0.5–2.5 mg/kg as a 0.25% or 0.5% solution; maximum dose 1 mL/kg of 0.25% solution, 0.5 mL/kg of 0.5% solution (2.5 mg/kg).

Peripheral nerve block: 0.3–2.5 mg/kg as a 0.25% or 0.5% solution; maximum dose 1 mL/kg of 0.25% solution, 0.5 mL/kg of 0.5% solution.

Epidural block in surgery: using 0.5% preservative-free solution: 1–2.5 mg/kg.

Caudal block in surgery: using 0.5% preservative-free solution: 1–2.5 mg/kg.

Note: Use lower doses for debilitated patients or those with epilepsy or acute illness.

Contraindications: Local inflammation or infection, septicaemia, IV regional anaesthesia (e.g., Bier's block), use in IV infusions, spinal or epidural anaesthesia in patients taking anticoagulant therapy or with coagulation disorders, severe anaemia or heart disease, spinal or epidural anaesthesia in dehydrated or hypovolaemic patients, hypersensitivity to amide local anaesthetics

Precautions: Respiratory impairment, hepatic impairment, epilepsy, porphyria, myasthenia gravis

Hepatic impairment: Avoid (or reduce dose) in severe liver disease.

Renal impairment: No dosage adjustment necessary.

Adverse effects

- Generally, occurs only with excessive dosage or following intravascular injection
- Arrhythmias, dizziness, hypertension, hypotension, nausea, paraesthesia, urinary retention, vomiting, blurred vision, restlessness, tremors, somnolence, constipation, confusion, headache, oedema, erythema at injection site, petechiae, skin irritation, lightheadedness, neurotoxicity, seizures, arrhythmias, arachnoiditis, cardiac arrest, diplopia, nerve disorders, paraplegia, paresis, respiratory depression, hypersensitivity reactions

Interactions with other medicines (*indicates serious): Lidocaine, procainamide, *propranolol, quinidine

Notes: To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body weight

Lignocaine (Lidocaine)

ATC code: N01BB02

Injection, 2% (HCl) in 30-mL vial, LOU 2

Topical Spray, 2%, 4%, 10% (HCl), LOU 2

Indications and dose

Adult

Peripheral and sympathetic nerve block

Infiltration anaesthesia by local infiltration: Dose determined by patient's weight and nature of procedure, max. 200 mg, maximum dose or 500 mg if given in solutions containing adrenaline

The dosage should be adjusted according to response of the patient and site of administration. The lowest concentration and smallest dose producing the required effect should be given.

Paediatric

Local infiltration and peripheral nerve block, using 1% or 2% solution

Child: Up to 3 mg/kg (0.3 mL/kg of 1% solution and 0.15 mL/kg of 2% solution, maximum dose 200 mg), not repeated within 2 hours

Contraindications: Local inflammation or infection, septicaemia, spinal or epidural anaesthesia in patients taking anticoagulant therapy or with coagulation disorders, severe anaemia or heart disease, spinal or epidural anaesthesia in dehydrated or hypovolaemic patients, hypersensitivity to amide local anaesthetics

Precautions: Bradycardia, impaired cardiac conduction,

severe shock, respiratory impairment, renal impairment, hepatic impairment, epilepsy, porphyria, myasthenia gravis.

Hepatic impairment: Avoid (or reduce dose) in severe liver disease.

Renal impairment: Severe-use with caution.

Adverse effects:

- Adverse effects generally occur only with excessive dosage or following intravascular injection.
- Hypotension, lightheadedness, dizziness, blurred vision, restlessness, tremors, confusion, headache, paraesthesia, somnolence, constipation, nausea, vomiting, oedema, erythema at injection site, petechiae, skin irritation, seizures, arrhythmias, heart block, cardiac arrest, hypersensitivity reactions, and respiratory failure

Interactions with other medicines (*indicates serious)

- Interactions are less likely when lidocaine is used topically.
- *Acetazolamide, *atenolol, bupivacaine, *furosemide, *hydrochlorothiazide, lopinavir, *procainamide, *propranolol, *quinidine, suxamethonium, *timolol, *verapamil

Notes

- Solutions containing preservatives should not be used for spinal, epidural, caudal, or IV regional anaesthesia.
- Children and elderly or debilitated patients require smaller doses, commensurate with age and physical status.

Lignocaine (Lidocaine) + Epinephrine (Adrenaline)

ATC code: N01BB52

Dental cartridge, 2% (HCl) + epinephrine 1:80 000, 1.8-mL cartridge, LOU 3

Injection, 2% (HCl or sulphate) + epinephrine 1:200 000 in vial, LOU 3

Indications and dose

Adult and children over 12 years of age

Dental anaesthesia by nerve block or infiltration, oral infiltration and/or mandibular block

Initial dosages of 1.0–5.0 mL (1/2 to 21/2 cartridges) is usually effective

Normal healthy adults: Amount of lignocaine administered should be kept below 500 mg and should not exceed 7 mg/kg

Minor never block and infiltration, infiltration: Up to 150 mg/dose

Intercostals (per nerve): 20–50 mg (maximum 150 mg)

Pudendal: 100 mg

Major nerve block, paracervical (each side): 100 mg

Sciatic: 300 mg

Paediatric

Dental anaesthesia by nerve block or infiltration, oral infiltration and/or mandibular block

In children under 10 years of age, it is rarely necessary to administer more than one-half cartridge (0.9–1.0 mL or 18–20 mg of lignocaine) per procedure to achieve local anesthesia for a procedure involving a single tooth. In maxillary infiltration, this amount will often suffice to the treatment of two to three teeth.

Other local anaesthesia

Child all ages: Dose needs to be adjusted according to child's physical status and nature of procedure. The lowest effective dose and concentration should be used. Dose should not be repeated within 2 hours.

Maximum dose of lidocaine **with epinephrine** is 7 mg/kg/dose..

Contraindications

- Lignocaine: Local inflammation or infection, septicaemia, spinal or epidural anaesthesia in patients taking anticoagulant therapy or with coagulation disorders, severe anaemia or heart disease, spinal or epidural anaesthesia in dehydrated or hypovolaemic patients, hypersensitivity to amide local anaesthetics
- Epinephrine: Cerebral arteriosclerosis, hypersensitivity to sympathomimetic amines

Precautions

- Lignocaine: Bradycardia, impaired cardiac conduction, severe shock, respiratory impairment, renal impairment, hepatic impairment, epilepsy, porphyria, myasthenia gravis, avoid for ring block of digits or appendages (risk of ischaemic necrosis)
- Epinephrine: Hypertension, heart block, heart disease, arrhythmias, cerebrovascular disease, thyroid disease, diabetes mellitus

Hepatic impairment: Lidocaine: Avoid (or reduce dose) in severe liver disease.

Renal impairment: Lidocaine: Severe - use with caution.

Pregnancy: Should be avoided in early pregnancy unless benefits outweigh risks

Breastfeeding: Not known to be harmful

Adverse effects

- Adverse effects generally occur only with excessive dosage or following intravascular injection.
- Hypotension, bradycardia, lightheadedness, dizziness, blurred vision, restlessness, tremors, confusion, headache, paraesthesia, somnolence, constipation, nausea, vomiting, oedema, erythema at injection site, petechiae, skin irritation, seizures, arrhythmias, heart block, cardiac arrest, hypersensitivity reactions, respiratory failure

Interactions with other medicines (*indicates serious)

- Interactions less likely when lidocaine is used topically.

- Lignocaine: *Acetazolamide, *atenolol, bupivacaine, *furosemide, *hydrochlorothiazide, lopinavir, *procainamide, *propranolol, *quinidine, suxamethonium, *timolol, *verapamil
- Adrenaline: Tricyclic antidepressants, MAOIs, general anaesthetic agents including halothane, oxytocic drugs of the ergot type, phenothiazines and butyrophenones, non-cardio-selective betablockers

Notes

- Lignocaine with adrenaline should not be administered intravenously or intra-arterially.
- Before injecting for local anaesthesia, syringe plunger should be withdrawn to make sure that injection is not into a vein or artery.
- Preservative-free solutions should be used for epidural or caudal use.
- Should not be used in digits and appendages, such as fingers, toes, ears, nose, and penis, because of risk of ischaemic necrosis.

1.3. Pre- & Intra-Operative Medication & Sedation For Short-Term Procedures & Adjuncts for Spinal & Epidural Anaesthesia

Dantrolene

ATC code: M03CA01

Injection, 20 mg, LOU 4

Indications and dose

Adult

Malignant hyperthermia, by rapid IV injection: Initially 2–3 mg/kg, then 1 mg/kg, repeated, if necessary, maximum 10 mg/kg per course

Paediatric

Malignant hyperthermia, by rapid IV injection

Child: Initially 2–3 mg/kg, then 1 mg/kg, repeated, if necessary, maximum 10 mg/kg per course

Child 5–11 years: Initially 500 micrograms/kg once daily for 7 days, then increased to 500 micrograms/kg/dose 3 times a day, then increased in steps of 500 micrograms/kg/dose every 7 days (max. per dose 2 mg/kg 3–4 times a day) until satisfactory response, maximum 400 mg per day

Child 12–17 years: Initially 25 mg once daily for 7 days, then increased to 25 mg 3 times a day, then increased in steps of 500 micrograms/kg/dose every 7 days (max. per dose 2 mg/kg 3–4 times a day) until satisfactory response, maximum 400 mg per day
Contraindications: None documented with IV use.

Precautions:

With IV use avoid extravasation, history of liver disorders (hepatotoxicity), if doses greater than 400 mg daily (hepatotoxicity), impaired cardiac function, impaired pulmonary function, patients over 30 years (hepatotoxicity), therapeutic effect may take a few weeks to develop - discontinue if no response within 6–8 weeks

Pregnancy: Use only if potential benefit outweighs risk.

Breastfeeding: Present in milk—use only if potential benefit outweighs risk.

Adverse effects: General: Abdominal pain, hepatic disorders, nausea, respiratory disorders, skin reactions, speech disorder, vomiting, chills, confusion, depression, eosinophilia, fever, headache, insomnia, nervousness, pericarditis, visual impairment, crystalluria, hyperhidrosis, arrhythmias, dizziness, drowsiness. Specific with IV use: GI haemorrhage, heart failure, localised pain, pulmonary oedema, seizure, and thrombophlebitis

Interactions with other medicines: CCBs (diltiazem, verapamil)

Notes: Should only be administered by or under the direct supervision of personnel experienced in the use of dantrolene when used for malignant hyperthermia.

Dexmedetomidine

See Section 1.1.2: Injectable Medicines (IV Anaesthetic Agents and Sedatives)

Ephedrine

ATC code: C01CA26

Injection, 30 mg (as HCl) per 1 mL, LOU 4

Indications and dose

Adult

Reversal of hypotension from spinal or epidural anaesthesia by slow IV injection: 3–6 mg every 3–4 minutes (max. per dose 9 mg), adjusted according to response, injection solution to contain ephedrine HCl 3 mg/mL, maximum 30 mg per course

Paediatric

Reversal of hypotension from spinal or epidural anaesthesia by slow IV injection

Child 1–11 years: 500–750 micrograms/kg every 3–4 minutes, adjusted according to response, alternatively 17–25 mg/m2 every 3–4 minutes, adjusted according to response, injection solution to contain ephedrine HCl 3 mg/mL, maximum 30 mg per course

Child 12–17 years: 3–7.5 mg every 3–4 minutes (max per dose 9 mg), adjusted according to response, injection solution to contain ephedrine HCl 3 mg/mL, maximum 30 mg per course

Directions for administration: For slow IV injection, give via central venous catheter (CVC) using a solution containing ephedrine HCl 3 mg/mL.

Contraindications: Hypersensitivity to ephedrine HCl in combination with:

- Other indirect sympathomimetic agents, such as phenylpropanolamine, phenylephrine, pseudoephedrine, and methylphenidate
- In combination with alpha sympathomimetic agents

» In combination with non-selective MAOIs or within 14 days of their withdrawal

Precautions: Diabetes mellitus, elderly, hypertension, hyperthyroidism, ischaemic heart disease, prostatic hypertrophy (risk of acute urinary retention)

Renal impairment: Use with caution.

Pregnancy: Increased foetal heart rate reported with parenteral ephedrine.

Breastfeeding: Present in milk, manufacturer advises to avoid - irritability and disturbed sleep reported

Adverse effects: Anxiety, arrhythmias, asthenia, confusion, depression, dyspnoea, headache, hyperhidrosis, insomnia, irritability nausea, palpitations, vomiting, acute urinary retention, acute angle closure glaucoma, angina pectoris, appetite decreased, cardiac arrest, dizziness, hypokalaemia, intracranial haemorrhage, psychotic disorder, pulmonary oedema, tremor

Interactions with other medicines (*indicates serious): *Indirect sympathomimetic agents (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate), *alpha sympathomimetics (oral and/or nasal route of administration), *non-selective MAOIs, ergot alkaloids, linezolid, tricyclic antidepressants (e.g., imipramine), noradrenergic-serotoninergic antidepressants (venlafaxine), theophylline, methyldopa, corticosteroids, antiepileptics, doxapram, oxytocin

Epinephrine (Adrenaline)

ATC code: C01CA24

Injection, 1mg /1mL amp, LOU 4

Indications and dose

Adult

Acute hypotension despite fluid therapy or anaphylactic reaction unresponsive to epinephrine IM

Add 4 ml of adrenaline (4 amp. of 1 mg/ml for IV route) to 36 ml of NaCl 0.9% or D5% to obtain a 0.1 mg/ml (100 micrograms/ml) solution.

Administer by continuous IV infusion using an infusion or syringe pump:

Paediatric

Child and adult: 0.1 microgram/kg/min, increase if necessary by 0.05 micrograms/kg/min every 10 min for the first hour, then every hour (max. 1 microgram/kg/min)

Once desired response is achieved, discontinue gradually, in decrements of 0.05 micrograms/kg/min every hour. Do not discontinue abruptly.

Acute hypotension despite fluid therapy or anaphylactic reaction unresponsive to epinephrine IM

Child < 40 kg: add 2 ml of adrenaline (2 amp. of 1 mg/ml for IV route) to 38 ml of NaCl 0.9% or D5% to obtain a 0.05 mg/ml (50 micrograms/ml) solution.

Child > 40 kg: add 4 ml of adrenaline (4 amp. of 1 mg/ml for IV route) to 36 ml of NaCl 0.9% or D5% to obtain a 0.1 mg/ml (100 micrograms/ml) solution.

Contraindications: Non-anaphylactic shock, narrow-angle glaucoma, co-administration during general anesthesia with halogenated hydrocarbons or cyclopropane, Labor, situations where vasopressors may be contraindicated, including thyrotoxicosis, diabetes, maternal blood pressure in excess of 130/80 mm Hg in hypertension and other cardiovascular disorders

Precautions: Administer with caution to patients with hypertension, angina, ischaemic heart disease, hyperthyroidism and to older patients.

Adverse effects: may cause arrhythmia, hypertension, agitation, headache, tissue necrosis following extravasation (use a large vein for IV administration).

Interactions with other medicines (*indicates serious): procainamide, quinidine, selegiline transdermal, sotalol, *amiodarone, *amitriptyline, *artemether lumefantrine, *lumefantrine, *chlorpromazine, *clarithromycin,*erythromycin, *fluconazole, *fluphenazine, *formoterol, *haloperidol, *imipramine, *isoflurane, *sevoflurane, *ketamine, *ketoconazole, *levoketoconazole

Fentanyl

ATC code: N01AH01

Injection (as citrate), 50 micrograms/mL (2-mL amp), LOU 4

Indications and dose

Adults and children aged 12 years and above: Restricted for intra-operative use only; rapid onset, short-acting; may also be adjunct to spinal anaesthesia

Spontaneous respiration: Analgesia and enhancement of anaesthesia during operation

» *By slow IV injection:* Initially, 50–100 micrograms (maximum per dose 200 micrograms); supplemental, 25–50 micrograms as required

» *By IV infusion:* 3–4.8 micrograms/kg/hour, adjusted according to response

Assisted ventilation: Analgesia and enhancement of anaesthesia during operation and analgesia and respiratory depression in intensive care

» *By slow IV injection*: Initially, 300–350 micrograms; supplemental, 100–200 micrograms as required

» *By IV infusion:* 10 micrograms/kg, dose to be given over 10 minutes, then 6 micrograms/kg/hour, adjusted according to response; may require up to 180 micrograms/kg/hour during cardiac surgery

Paediatric

Spontaneous respiration: Analgesia and enhancement of anaesthesia during operation, by IV injection

Child 1 month–11 years: Initially 1–3 micrograms/kg, then 1 microgram/kg as required, dose to be administered over at least 30 seconds

Child 12–17 years: Initially 50–100 micrograms (max. per dose 200 micrograms), then 25–50 micrograms as required, dose to be administered over at least 30 seconds

Assisted ventilation: Analgesia and enhancement of anaesthesia during operation by IV injection

Neonate: Initially, 1–5 micrograms/kg, then 1–3 micrograms/kg as required, dose to be administered over at least 30 seconds

Child 1 month–11 years: Initially 1–5 micrograms/kg, then 1–3 micrograms/kg as required, dose to be administered over at least 30 seconds

Child 12–17 years: Initially 1–5 micrograms/kg, then 50–200 micrograms as required, dose to be administered over at least 30 seconds

Assisted ventilation: Analgesia and respiratory depression in intensive care by IV injection

Neonate: Initially, 1–5 micrograms/kg, then by IV infusion, 1.5 micrograms/kg/hour, adjusted according to response.

Child: Initially 1–5 micrograms/kg, then by IV infusion, 1–6 micrograms/kg/hour, adjusted according to response

Contraindications: Hypersensitivity to the active substance or to any of the excipients, known intolerance to fentanyl or other morphino-mimetics, respiratory depression, obstructive airway disease, in patients after operative interventions in the biliary tract

Precautions: Repeated intraoperative doses should be given with care because the resulting respiratory depression can persist post-operatively.

Adverse effects: hypersensitivity reactions, muscle rigidity, bradycardia, tachycardia, arrhythmia, hypotension, hypertension, venous pain

Interaction with other medicines: Barbiturates, benzodiazepines, neuroleptics, other non-selective CNS depressants (e.g., alcohol), beta-blockers, suxamethonium, halothane, vecuronium, IV midazolam

Ketamine

See Section 1.1.2, Injectable Medicines (IV Anaesthetic Agents and Sedatives)

Midazolam

See Section 1.1.2, Injectable Medicines (IV Anaesthetic Agents and Sedatives)

Morphine

ATC code: N02AA01

Injection, 10 mg (as sulphate or HCl) in 1 mL amp, LOU 4

Injection, 10 mg (preservative free) in 1 mL amp, LOU 5

Indications and dose

Adult

- Preoperative sedative and analgesic
- Loading doses of typically between 1 mg and 10 mg (maximum 15 mg) of morphine sulphate may be given by IV infusion over 4 or 5 minutes. The loading dose used will depend upon the patient's diagnosis and condition.

Paediatric

IV

Infant or **child:** 0.05–0.1 mg/kg 5 minutes before the procedure; maximum dose 15 mg

IM

Infant or **child:** 0.1 mg/kg 20 minutes before the procedure; maximum dose 15 mg

Only use IM route for premedication if patient has no IV access and adequate respiratory monitoring is available.

Contraindications: Respiratory depression, severe respiratory disease, CNS depression, risk of paralytic ileus, raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma

Precautions

- Renal impairment, hepatic impairment, dependence (severe withdrawal symptoms if withdrawn abruptly), hypothyroidism, convulsive disorders, decreased respiratory reserve and acute asthma, hypotension, prostatic hypertrophy, overdosage.
- Skilled tasks: Warn patient or caregiver about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike or operating machinery, for 24 hours.

Hepatic impairment: Avoid or reduce dose, may precipitate coma

Renal impairment: Moderate to severe—reduce dose or avoid, increased and prolonged effect, increased cerebral sensitivity

Adverse effects: Nausea, vomiting, constipation, lightheadedness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, anorexia, spasm of urinary and biliary tract, pruritus, rash, postural hypotension, miosis, respiratory depression (dose related), bradycardia, tachycardia, palpitations, syndrome of inappropriate antidiuretic hormone secretion (SIADH), anaphylaxis.

Interactions with other medicines (*indicates serious): Amitriptyline, chlorpromazine, ciprofloxacin, diazepam, haloperidol, metoclopramide, *ritonavir

Notes

- For IV administration, administer slowly over 5 minutes.
- **Overdose: Risk of small children receiving ten times the dose. Extreme care required with dose calculation and preparation.**

Ondansetron

ATC code: A04AA01

Injection 2 mg (as HCl)/mL (2-mL amp), LOU 4

Indications and dose

Adult

Prevention of postoperative nausea and vomiting, 4 mg IV/IM immediately before anesthesia or after procedure or 16 mg PO 1 hr before anesthesia; patients >80 kg may need additional 4 mg IV

Paediatric

Prevention of postoperative nausea and vomiting

Child 6 month–18 years: By slow IV injection over at least 30 seconds, 100 micrograms/kg (max. 4 mg) before, during, or after induction of anaesthesia. Treatment of postoperative nausea and vomiting by IM or slow IV injection

Child 6 month–18 years: By slow IV injection over at least 30 seconds, 100 micrograms/kg (max. 4 mg)

Contraindications: Hypersensitivity to the active substance or to other selective 5-HT3 receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients

Precautions: Respiratory events could be precursors of hypersensitivity reactions, prolongs the QT interval in a dose-dependent manner, may cause myocardial ischemia, Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration, increases large bowel transit time, may mask occult bleeding.

Pregnancy: should not be used during the first trimester of pregnancy.

Breastfeeding: Not recommended during breastfeeding

Adverse effects: hypersensitivity reactions, anaphylaxis, headache, Sensations of flushing or warmth, constipation.

Interactions: Apomorphine, CYP3A4 inducers, tramadol

See section 3.3.1 for more information on ondansetron

Phenylephrine

ATC code: C01CA06

Injection, 10 mg/mL, LOU 5

Indications and dose

Adjunct medicine; used for intractable hypotension after epidural/spinal anaesthesia

Adult

By SC/IM injection: 2–5 mg with further doses of 1–10 mg if necessary, according to response

By slow IV injection: 100–500 micrograms as a 0.1% solution, repeated as necessary after at least 15 minutes

By IV infusion: 10 mg in 500 mL of glucose 5% injection or sodium chloride 0.9% injection, initially at a rate of up to 180 micrograms per minute, reduced according to response to 30–60 micrograms/minute

Paediatric

By SC injection or IM injection

Child 1–11 years: 100 micrograms/kg every 1–2 hours (max. per dose 5 mg) as required

Child 12–17 years: Initially 2–5 mg (max. per dose 5 mg), followed by 1–10 mg, after at least 15 minutes if required

By slow IV injection

Child 1–11 years: Initially 5–20 micrograms/kg (max. per dose 500 micrograms), repeated as necessary after at least 15 minutes

Child 12–17 years: 100–500 micrograms, repeated as necessary after at least 15 minutes

By IV infusion

Child 1–15 years: Initially 100–500 nanograms/kg/min, adjusted according to response

Child 16–17 years: Initially up to 180 micrograms/min, reduced to 30–60 micrograms/min, adjusted according to response

Contraindications: Patients taking MAOIs, or within 14 days of ceasing such treatment, severe hypertension, and hyperthyroidism, avoid in patients with prostatic enlargement

Pregnancy and breastfeeding: Use only if potential benefit outweighs risk

Adverse effects: Reflex bradycardia, hypotension, dizziness, syncope, flushing, headache, cerebral haemorrhage, paraesthesia, mydriasis, eodema, palpitations, hypersalivation.

Interactions with other medicines: See Epinephrine, Section 4

Propofol

See Section 1.1.2, Injectable Medicines (IV Anaesthetic Agents and Sedatives)

Remifentanyl

See Section 1.1.2, Injectable Medicines (IV Anaesthetic Agents and Sedatives)

1.4. Medical Gases

Medical Air

ATC code: V03AN05

Inhalation (medical gas), LOU 4

Indications: As a carrier for some anesthetic agents; to provide clean air in ventilators and incubators; to power air driven medical equipment, such as resuscitators

Contraindications: None

Precautions: None

Adverse effects: None

Interaction with other medicines: None

Nitrous oxide

ATC code: N01AX13

Inhalation (medical gas), LOU 4

Indications and dose

Adult

Maintenance of anaesthesia in combination with other anaesthetic agents and muscle relaxants: Administration by inhalation, nitrous oxide mixed with 25–30% oxygen

Analgesia for emergency management of injuries, during postoperative physiotherapy, and for refractory pain in terminal illness: Administration by inhalation, 50% nitrous oxide mixed with 50% oxygen

Maintenance of light anaesthesia: Administration by inhalation, nitrous oxide mixed with 25–30% oxygen; analgesia, 50% nitrous oxide mixed with 50% oxygen

Paediatric

Neonate, infant, or **child:** *Administration through inhalation for anaesthetic:* Up to 66% in oxygen

Analgesia, administration through inhalation: Up to 50% in oxygen, according to the child's needs

Contraindications: Demonstrable collection of air in pleural (pneumothorax), pericardial or peritoneal space, intestinal obstruction, occlusion of middle ear, arterial air embolism, decompression sickness, chronic obstructive airway disease, emphysema

Precautions

- Minimize exposure of staff, vitamin B_{12} deficiency
- Nitrous oxide may have a deleterious effect if used in patients with an air-containing closed space since nitrous oxide diffuses into such a space with a resulting increase in pressure. This effect may be dangerous in conditions such as pneumothorax, which may enlarge to compromise respiration or in the presence of intracranial air after head injury, entrapped air following recent underwater dive, or recent intraocular gas injection.

Hepatic and renal impairment: No dosage adjustment necessary

Adverse effects

- Hypotension, arrhythmias, confusion, dizziness, headache, nausea, vomiting, and apnea
- Malignant hyperthermia, after prolonged administration: Megaloblastic anaemia, leukopenia, agranulocytosis, neuropathy, and myeloneuropathy

Interactions with other medicines (*indicates serious): Amitriptyline, *chlorpromazine, diazepam, enalapril, *fluphenazine, furosemide, *haloperidol, isoniazid, *methotrexate, spironolactone, vancomycin, *verapamil

Notes

- Should not be used as a sole anaesthetic agent due to lack of potency
- Oxygen should be administered after use to avoid diffusional hypoxia.

Oxygen

ATC code: V03AN01

Inhalation (medicinal gas), LOU 2

Indications and dose

- Maintain adequate tissue oxygenation in inhalational anaesthesia and other indications for use in neonates and children.
- Used during resuscitation and for treating respiratory problems requiring supplemental oxygen.
- Concentration of oxygen in inspired anaesthetic gases should never be <29–30%. The concentration required depends on the condition being treated.

Contraindications: None

Precautions: None

Hepatic and renal impairment: No dosage adjustment necessary

Adverse effects

- Long-term use of concentrations >80% have a toxic effect on the lungs, leading to pulmonary congestion, exudation, and atelectasis. Short-term use of 100% is not associated with these toxic effects.
- Inappropriate concentration may have serious or even lethal effects, e.g., morbidity, brain damage, and, especially in pre-term neonates, can cause retinopathy with blindness and chronic lung disease.

Interactions with other medicines (*indicates serious): *Bleomycin

Notes

- Monitoring of oxygen delivered is strongly recommended.
- An oxygen analyzer should be used to monitor inspired oxygen. A pulse oximeter is mandatory to monitor oxygen saturation.
- Oxygen should be added routinely during anaesthesia with inhalational agents, even when air is used as the carrier gas, to protect against hypoxia.
- Use of 100% oxygen should not be withheld in an emergency situation.
- Fire hazard: reducing valves on oxygen cylinders must not be greased (risk of explosion).

2. Muscle Relaxants (Peripherally Acting) & Cholinesterase Inhibitors & Anticholinergics

2.1. Muscle Relaxants

Atracurium

ATC code: M03AC04

Injection, 10 mg (as besilate)/mL (5-mL amp), LOU 4

Indications and dose

Adult

Neuromuscular blockade (short to intermediate duration) for surgery and intubation by IV injection: Initially 300–600 micrograms/kg, then by IV injection 100–200 micrograms/kg as required; alternatively, by IV injection initially 300–600 micrograms/kg, followed by IV infusion 300–600 micrograms/kg/hour

Neuromuscular blockade during intensive care by IV injection: Initially 300–600 micrograms/kg, initial dose is optional, then by IV infusion 270–1770 micrograms/kg/hour

By IV infusion: Usual dose 650–780 micrograms/kg/hour

Paediatric

Neuromuscular blockade (short to intermediate duration) for surgery and intubation

Child: Initially by IV injection 300–600 micrograms/kg, then by IV injection 100–200 micrograms/kg repeated if necessary; alternatively, by IV injection initially 300–600 micrograms/kg, followed by IV infusion 300–600 micrograms/kg/hour, adjusted according to response

Neonate: Initially by IV injection 300–500 micrograms/kg, followed by IV injection 100–200 micrograms/kg, repeated if necessary; alternatively, by IV infusion 300–400 micrograms/kg/hour, adjusted according to response

Neuromuscular blockade during intensive care

Child: Initially by IV injection 300–600 micrograms/kg, initial dose is optional, then by IV infusion 270–1770 micrograms/kg/hour; by IV infusion usual dose 650–780 micrograms/kg/hour

Neonate: Initially by IV injection 300–500 micrograms/kg, followed by IV injection 100–200 micrograms/kg, repeated if necessary; alternatively, by IV infusion 300–400 micrograms/kg/hour, adjusted according to response; higher doses may be necessary

Adverse effects: Seizure, cardiac arrest

Interactions: Neuromuscular blocking drugs: non-depolarising, aminoglycosides, beta-blockers, clindamycin, CCBs, ketamine, lidocaine, loop diuretics, theophylline, and symphathomimetics

Notes

- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body weight.
- Hypotension, skin flushing, and bronchospasm are associated with histamine release. To minimise effects of histamine release, administer over 1 minute in patients with cardiovascular disease or sensitivity to hypotension.
- For IV infusion, give continuously in glucose 5% or sodium chloride 0.9%; stability varies with diluent; dilute requisite dose with infusion fluid to a concentration of 0.5–5 mg/mL.

Cisatracurium

ATC code: M03AC11

Injection, 2 mg (as besilate)/mL (10-mL amp), LOU 4

Indications and dose

Adult

Neuromuscular blockade (intermediate duration) during surgery and intubation by IV injection: Initially 150 micrograms/kg, then by IV injection maintenance 30 micrograms/kg every 20 minutes; alternatively, by IV infusion initially 180 micrograms/kg/hour, then by IV infusion maintenance 60–120 micrograms/kg/hour; maintenance dose administered after stabilization

Neuromuscular blockade (intermediate duration) during intensive care by IV injection: Initially 150 micrograms/kg, initial dose is optional, then by IV infusion 180 micrograms/kg/hour, adjusted according to response; by IV infusion usual dose 30–600 micrograms/kg/hour

Paediatric

Neuromuscular blockade (intermediate duration) during surgery and intubation and intensive care, IV

Child 1 month–1 year: Initially 150 micrograms/kg, then by IV injection 30 micrograms/kg every 20 minutes as required

Child 2–11 years: Initially 150 micrograms/kg, 80–100 micrograms/kg if not for intubation, then by IV injection 20 micrograms/kg every 10 minutes as required; alternatively, by IV injection initially 150 micrograms/kg, followed by IV infusion 180 micrograms/kg/hour, by IV infusion reduced to 60–120 micrograms/kg/hour, adjusted according to response

Child 12–17 years: Initially 150 micrograms/kg, then by IV injection 30 micrograms/kg every 20 minutes as required; alternatively, by IV injection initially 150 micrograms/kg, followed by IV infusion 180 micrograms/kg/hour, by IV infusion reduced to 60–120 micrograms/kg/hour, adjusted according to response

Adverse drugs reactions: Bradycardia, hypotension, bronchospasms, flushing, rash

Interactions: Neuromuscular blocking drugs, non-depolarizing

Notes

» **Directions for administration:** For IV infusion, given continuously in glucose 5% or sodium chloride 0.9%, solutions of 2 mg/mL may be infused undiluted, alternatively dilute with infusion fluid to a concentration of 0.1–2 mg/mL.

» Doses at extremes of body weight: To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body weight

Rocuronium

ATC Code: M03AC09

Dose form, Injection, 10mg/mL,(as bromide), 5 ml Vial, LoU 5

Indications and dose

Adults

Dose should be calculated based on body weight.

Rapid Sequence Intubation: 0.6-1.2 mg/kg IV

Tracheal Intubation: 0.45-0.6 mg/kg IV

Maintenance dose: 0.1-0.2 mg/kg IV repeat PRN OR

Continuous infusion: 0.01-0.012 mg/kg/min IV

Paediatrics

Same as adults for intubation during routine anaesthesia and maintenance dose.

Duration of action of the single intubating dose will be longer in neonates and infants than in children.

Contraindications: Hypersensitivity, Lack of ventilatory support, neuromuscular disease, Other neuromuscular blocking agents

Precautions: Adequate facilities and staff for endotracheal intubation and artificial ventilation should be available, precaution to address anaphylactic reactions, tachycardia, closely monitor patient, myopathy, patients with neuromuscular disease,

Hepatic & renal impairment: Use with caution.

Pregnancy: Use with caution

Breastfeeeding: benefits should outweigh the risks

Adverse effects: Transient hypotension, Hypertension, Dose-related tachycardia, Apnea, Abnormal ECG, Injection site edema, Hiccups, Pruritus, Nausea, Wheezing, Residual muscle weakness, Allergic or idiosyncratic hypersensitivity reactions

Interactions with other medicines medicines (*indicates serious): *Amikacin, *amphotericin B deoxycholate, *benzhydrocodone/paracetamol, *capreomycin, *clindamycin, *colistin, *doxycycline, *fentanyl, *fentanyl intranasal, *fentanyl transmucosal, *lincomycin, *gentamicin, *hydrocodone, *minocycline,*paromomycin, *polymyxin B, *quinine, *tetracycline, *tobramycin.

Suxamethonium

ATC code: M03AB01

Injection, 50 mg (chloride)/mL in 2-mL amp, LOU 4

Indications and dose: Skeletal muscle relaxation in procedures of short duration, such as endotracheal intubation or endoscopy

Adult

Muscle relaxation (prolonged procedures) by IV infusion: 2.5–4 mg/min of solution containing 1–2 mg/mL, maximum, 500 mg/hour

Muscle relaxation by IV injection: 1 mg/kg, followed, if necessary, by supplements of 0.5–1 mg/kg at 5–10-minute intervals

Paediatric

Muscle relaxation (neuromuscular blockade) in procedures of short duration

IM

Neonate or **infant:** Up to 4–5 mg/kg produces a 10–30-minute paralysis (after 2–3-minute delay)

Child: Up to 4 mg/kg produces a 10–30-minute paralysis (after 2–3-minute delay); maximum dose 150 mg

IV

Neonate: 2 mg/kg produces 5–10-minute paralysis, 3 mg/kg results in full neuromuscular block

Infant: Initially 2 mg/kg; maintenance is usually 1–2 mg/kg at 5–10-minute intervals as necessary

Child: Initially 1 mg/kg, then 0.5–1 mg/kg repeated every 5–10 minutes as necessary

Contraindications: Inability to maintain clear airway, personal or family history of malignant hyperthermia, neurological disease involving acute wasting of major muscle, skeletal myopathies, prolonged immobilization, personal or family history of congenital myotonic disease, Duchenne muscular dystrophy or low plasma cholinesterase activity (including severe liver disease), myasthenia gravis, glaucoma, ocular surgery, penetrating eye injury, liver disease, burns, personal or family history of prolonged paralysis or apnoea with the use of depolarizing muscle relaxants, recent multiple trauma or spinal cord injury

Precautions: Digitalis toxicity or recent digitalization, cardiac, respiratory or neuromuscular disease, paraplegia, severe sepsis, prolonged apnoea on repeated injection (infusion preferred for long surgical procedures), hyperkalaemia, renal impairment

Renal impairment: Severe—dose reduction not required but use with caution.

Hepatic impairment: Avoid use in severe hepatic impairment. Prolonged apnoea may occur in liver disease due to reduced hepatic synthesis of pseudocholinesterase.

Adverse effects: Post-operative muscle pain, muscle fasciculations prior to paralysis, increased salivary, bronchial and gastric secretions, transient rise in intragastric pressure, increased intraocular pressure, bradycardia (particularly with repeated dosing), hypotension, arrhythmias, hyperkalaemia, myoglobinuria, myoglobinaemia, hypersensitivity reactions (including flushing, rash, urticaria, bronchospasm and shock), malignant hyperthermia (may be fatal)

Interactions with other medicines (*indicates serious): *Amikacin, *capreomycin, cyclophosphamide, digoxin,

*gentamicin, halothane, lidocaine, lithium, magnesium (parenteral), metoclopramide, neostigmine, *paromomycin, procainamide, propranolol, pyridostigmine, *quinine, *streptomycin

Notes

- Also referred to as succinylcholine
- Usually administered after anaesthetic induction
- Neonates and young infants are less sensitive to suxamethonium and higher doses may be required.
- Administration: For IV injection, give undiluted, or dilute with glucose 5% or sodium chloride 0.9%.
- Premedication with atropine reduces bradycardia and excessive salivation.
- Manufacturer's instructions on storage conditions should be followed. Solution form of injection should be refrigerated; room temperature stability is product-specific.

Vecuronium

ATC code: M03AC03

Powder for injection, 10 mg (bromide) in vial, LOU 6

Indications and dose

Adult

Intubation, by IV injection, initially 80-100 micrograms/kg, usual maintenance dose, 20-30 micrograms/kg

Muscle relaxation, by IV infusion: Initially, 40–100 micrograms/kg, then 0.8–1.4 micrograms/kg/min

Paediatric

Intubation

Child 1–4 months: Initially 10–20 micrograms/kg, followed by incremental doses according to response

Child over 5 months: *by IV injection*: Initially 80–100 micrograms/kg, usual maintenance dose, 20–30 micrograms/kg

Muscle relaxation during surgery, by IV infusion

Neonate: Initially 80–100 micrograms/kg, then 30–50 micrograms/kg adjusted according to response.

Infant or Child**:** Initially 80–100 micrograms/kg, then either by IV injection 20–30 micrograms/kg repeated as required, or by IV infusion 50–80 micrograms/kg per hour, adjusted according to response

Precautions: Hepatic impairment, possibly increase dose in patient with burns, electrolyte disturbances, possibly decrease dose in respiratory acidosis, hypokalaemia and hypothermia, history of asthma, severe obesity (maintenance of adequate airway and ventilation support), neuromuscular disease, myasthenia gravis, renal impairment

Renal impairment: Dose reduction not necessary, yet duration of action may be prolonged in renal impairment; use cautiously.

Hepatic impairment: Dose reductions are necessary in patients with cirrhosis or cholestasis. Impairment decreases clearance resulting in prolonged duration of action.

Adverse effects: Hypersensitivity reactions, including bronchospasm, hypotension, tachycardia, oedema, erythema, pruritus

Interactions with other medicines (*indicates serious): *Amikacin, carbamazepine, *capreomycin, *clindamycin, *gentamicin, halothane, neostigmine, phenytoin, *procainamide, propranolol, pyridostigmine, *quinidine, *streptomycin

Notes

- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body weight.
- Vecuronium may be supplied with diluent containing benzyl alcohol. Sterile water for injection should be used to reconstitute for neonates.

2.2. Cholinesterase Inhibitors

Neostigmine

ATC code: N07AA01

Injection, 2.5 mg (metilsulphate) in 1-mL amp, LOU 4

Indications and dose

Adult

Myasthenia gravis, by SC or IM injection: 1–2.5 mg as required, usual total daily dose, 5–20 mg

Reversal of non-depolarizing block by IV injection: Over 1 minute, 2.5 mg, followed, if necessary, by supplements of 500 micrograms to maximum total dose of 5 mg

Post-operative urinary retention, by SC or IM injection: 500 micrograms; catheterization required if urine not passed within 1 hour

Paediatric

Treatment of myasthenia gravis (using neostigmine metilsulphate), SC or IM

Neonate: 150 micrograms/kg every 6–8 hours, 30 minutes before feeds, increased to a maximum of 300 micrograms/kg every 4 hours, if necessary

Infant or **child:** 200–500 micrograms repeated at suitable intervals throughout the day

Reversal of non-depolarizing muscle block (using neostigmine metilsulphate), IV over 1 minute

Neonate: 50–80 micrograms/kg, after or with atropine.

Infant or **child:** 50–80 micrograms/kg (maximum 2.5 mg) after or with atropine

Contraindications: Recent intestinal or bladder surgery, mechanical intestinal or urinary tract obstruction, after suxamethonium, pneumonia, peritonitis

Precautions: Asthma, urinary tract infection, cardiovascular disease, including arrhythmias, bradycardia, vagotonia, recent MI or atrioventricular block, hyperthyroidism, hypotension, peptic ulcer,

epilepsy, renal impairment

Renal impairment

Mild to moderate: Administer 50% of normal dose.

Severe: Administer 25% of normal dose.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Increased salivation, nausea, vomiting, abdominal cramps, diarrhoea, bradycardia, Thrombophlebitis, rash associated with bromide salt, signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus, heart block, arrhythmias, hypotension, agitation, excessive dreaming, weakness eventually leading to fasciculation and paralysis.

Interactions with other medicines (*indicates serious): Amikacin, atropine, chloroquine, clindamycin, gentamicin, paromomycin, propranolol streptomycin, suxamethonium, vecuronium

Notes

- Simultaneous administration of an antimuscarinic drug, such as atropine, may be required to reduce the muscarinic adverse effects of neostigmine; however, it is not used routinely in treatment of myasthenia gravis, as it can mask the signs of overdose.
- **Directions for administration:** For IV injection, given undiluted or diluted with glucose 5% or sodium chloride 0.9% or water for injections.

Pyridostigmine

ATC code: N07AA02

Injection, 5mg/mL, 2mL LOU 6

Tablet, 60 mg (bromide), LOU 5

Oral solution, 60 mg/5 mL, LOU 6

Indications and dose

Adult

Myasthenia gravis, oral: Initially 30–120 mg at suitable intervals throughout the day, gradually increased until desired response is obtained, usual total daily dose within range, 0.3–1.2 g, given at appropriate intervals when high doses are required (doses above 450 mg daily are not usually advisable in order to avoid acetylcholine receptor down regulation)

Paediatric

Myasthenia gravis, oral

Neonate: Initially 1–1.5 mg/kg, increased gradually to maximum of 10 mg, every 4–6 hours; give dose 30–60 minutes before feeds

Infant or **child:** Initially 1–1.5 mg/kg daily increased gradually to 7 mg/kg daily in 6 divided doses; usual total daily dose is 30–360 mg

Myasthenia Gravis, IV/IM

Children: 0.05-0.15 mg/kg every 4 to 6hours; not to exceed 10 mg/dose

Neonates: 0.05-0.15 mg/kg every 4 to 6hours; not to exceed 10 mg/dose

Reversal of non-depolarizing muscle relaxants, IV

Child and Neonate: 0.1-0.25 mg/kg/dose

Dosing range: 0.1-0.25 mg/kg/dose; full recovery may occur as early as <15 min but may require >30 min

Contraindications: Recent intestinal or bladder surgery, mechanical intestinal or urinary tract obstruction, after suxamethonium, pneumonia, peritonitis

Precautions: Asthma, urinary tract infection, cardiovascular disease including arrhythmias, bradycardia, vagotonia, recent MI or atrioventricular block, hyperthyroidism, hypotension, peptic ulcer, epilepsy, renal impairment

Renal impairment: Use with caution. Dosage reduction may be required.

Hepatic impairment: Dosage adjustment considered unnecessary.

Adverse effects: Increased salivation, nausea, vomiting, abdominal cramps, diarrhoea, bradycardia, thrombophlebitis, rash associated with bromide salt, signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus, heart block, arrhythmias, hypotension, agitation, excessive dreaming, weakness eventually leading to fasciculation and paralysis.

Interactions with other medicines (*indicates serious): Amikacin, atropine, chloroquine, clindamycin, *gentamicin, *paromomycin, propranolol, *streptomycin, suxamethonium, vecuronium

Notes

- For treatment of myasthenia gravis, oral doses can be divided so that the patient receives the larger doses at the times of greatest fatigue.
- Given 30–60 minutes before feeds in babies to improve suckling but given after food or milk in older children/adults to reduce abdominal cramping.

2.3. Anticholinergics

Atropine

ATC code: A03BA01

Injection, 1 mg (as sulphate) in 1-mL amp, LOU 4

Indications and dose

Adult

Preoperative medication to inhibit salivation and secretions, reversal of the muscarinic effects of cholinergic agents, such as neostigmine and pyridostigmine; treatment of bradycardia secondary to cholinergic stimulation

Premedication by IV injection: 300–600 micrograms, to be administered immediately before induction of anaesthesia

By SC injection or IM injection: 300–600 micrograms, to be administered 30–60 minutes before induction of anaesthesia

Intra-operative bradycardia by IV injection: 300–600 micrograms, larger doses may be used in emergencies

Control of muscarinic adverse effects of neostigmine in reversal of competitive neuromuscular block, by IV injection: 0.6–1.2 mg

Excessive bradycardia associated with beta-blocker use, by IV injection: 0.6–2.4 mg in divided doses (max. per dose 600 micrograms)

Bradycardia following MI (particularly if complicated by hypotension) by IV injection: 500 micrograms every 3–5 minutes, maximum 3 mg per course

Paediatric

Premedication, IV

Child all ages: 20 micrograms/kg (max 600 micrograms) immediately before induction of anaesthesia

Premedication, SC

Neonate: 10–15 micrograms/kg 30–60 minutes before induction of anaesthesia

Infant or **child:** 20 micrograms/kg (minimum dose 100 micrograms, maximum dose

600 micrograms) 30–60 minutes before induction of anaesthesia

Premedication, IM

Infant or **child:** 20 micrograms/kg (minimum dose 100 micrograms, maximum dose 600 micrograms) 30–60 minutes before induction of anaesthesia

Reversal of the muscarinic effects of cholinergic agents, IV

Neonate: 20 micrograms/kg

Infant or **child:** 20 micrograms/kg (maximum dose 600 micrograms)

Treatment of bradycardia secondary to cholinergic stimulation, IV

Neonate: 20 micrograms/kg

Infant or **child:** 10–20 micrograms/kg (maximum dose 600 micrograms)

Contraindications: Closed-angle glaucoma, myasthenia gravis, prostatic enlargement, severe gastrointestinal (GI) inflammatory disease, GI obstruction

Precautions

- For IV administration, administer undiluted by rapid IV injection, slow injection may result in paradoxical bradycardia.
- Down syndrome, children, ulcerative colitis, diarrhoea, heart failure, GI disorders, hyperthyroidism, cardiac disorders, tachycardia, hypertension, hypoxia, fever and in warm environments (monitor temperature and keep patients cool), constipation, delirium
- Children are at increased risk for rapid rise in body temperature due to suppression of sweat gland activity. Large doses may cause paradoxical hyperexcitability.
- Down syndrome children have both increased sensitivity to cardiac effects and mydriasis.
- Children with Down syndrome also have more secretions and may require atropine more frequently.

Hepatic and renal impairment: Use with caution. No dose adjustment necessary.

Adverse effects: Dry mouth, blurred vision, photophobia, flushing and dryness of skin, rash, difficulty in micturition, constipation, arrhythmias, tachycardia, palpitations, fever, nausea, vomiting, confusion, closed-angle glaucoma, seizures

Interactions with other medicines (*indicates serious):

- Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase adverse effects, such as dry mouth, urine retention, and constipation.
- Amitriptyline, chlorpheniramine, chlorpromazine, haloperidol, metoclopramide, neostigmine, pyridostigmine

Glycopyrronium

ATC code: A03AB02

Injection, 200 micrograms (as bromide)/mL, LOU 4

Indications and dose

Adult

Premedication at induction by IM injection or by IV injection: 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms)

Intra-operative bradycardia by IV injection: 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms), repeated if necessary

Control of muscarinic adverse effects of neostigmine in reversal of non-depolarizing neuromuscular block by IV injection: 10–15 micrograms/kg, alternatively, 200 micrograms per 1 mg of neostigmine to be administered

Paediatric

Premedication at induction, by IM injection or by IV injection

Neonate: 5 micrograms/kg

Child 1 month–11 years: 4–8 micrograms/kg (max. per dose 200 micrograms)

Child 12–17 years: 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms)

Intra-operative bradycardia by IV injection

Neonate: 10 micrograms/kg, repeated if necessary

Child: 4–8 micrograms/kg (max. per dose 200 micrograms), repeated if necessary

Control of muscarinic adverse effects of neostigmine in reversal of non-depolarizing neuromuscular block, by IV injection

Neonate: 10 micrograms/kg

Child 1 month–11 years: 10 micrograms/kg (max. per dose 500 micrograms)

Child 12–17 years: 10–15 micrograms/kg, alternatively, 200 micrograms per 1 mg of neostigmine to be administered.

Adverse effects: Anhidrosis, bronchial secretion decreased, mydriasis

Interactions with other medicines: Anticholinergics, cyclopropane, ketoconazole potassium chloride

Note: Antimuscarinic drugs used for premedication to general anaesthesia should only be administered by or under direct supervision of personnel experienced in their use.

3. Medicines For Pain & Palliative Care

3.1. Non-Opioids & Non-Steroidal Anti-Inflammatory Medicines (NSAIMs)

Use NSAIMs with caution in patients with renal disease, peptic ulcer disease, and cardiovascular conditions.

Acetylsalicylic Acid (Aspirin)

ATC code: N02BA01

Tablet, 300 mg, LOU 2

Indications and dose

Adult

Pain, fever, and inflammation, mild to moderate pain, including dysmenorrhoea, headache, pain and inflammation in rheumatic disease, and other musculoskeletal disorders, including juvenile arthritis, pyrexia, acute migraine attack

Mild to moderate pain, pyrexia, oral: 300–900 mg every 4 to 6 hours if necessary, maximum, 4 g daily

Inflammatory arthritis, oral: 4 to 8 g daily in divided doses in acute conditions, up to 5.4 g daily may be sufficient in chronic conditions

Paediatric

Juvenile arthritis, rheumatic fever, oral

Infant or **child:** Up to 130 mg/kg daily in 5–6 divided doses in acute conditions; 80–100 mg/kg daily in divided doses for maintenance

Kawasaki disease, oral

Neonate: Initially 8 mg/kg four times daily until afebrile, followed by 5 mg/kg once daily for 6–8 weeks; if no evidence of coronary lesions after 8 weeks, discontinue treatment or seek expert advice.

Infant or **child:** Initially 7.5–12.5 mg/kg four times daily until afebrile, followed by 2–5 mg/kg once daily for 6–8 weeks; if no evidence of coronary lesions after 8 weeks, discontinue treatment or seek expert advice.

Contraindications: Hypersensitivity (including asthma, angioedema, urticaria, or rhinitis) to acetylsalicylic acid or any other NSAIM, previous or active peptic ulceration, children with or recovering from viral illnesses, haemophilia and other bleeding disorders; not to be used for the treatment of gout (only for simple analgesia)

Precautions: Asthma, uncontrolled hypertension, concomitant use of drugs that increase risk of bleeding, previous peptic ulceration, glucose-6-phosphate dehydrogenase (G6PD) deficiency, dehydration, renal impairment, hepatic impairment, pregnancy, breastfeeding, allergic disease, elderly.

Renal impairment: Increased risk of bleeding and acetylsalicylic acid induced renal impairment; severe—avoid; increased risk of sodium and water retention; deterioration in renal function; GI bleeding

Hepatic impairment: Avoid in severe hepatic impairment; increased risk of GI bleeding

Pregnancy: Avoid in last few weeks of pregnancy, high doses may be related to intrauterine growth restriction, teratogenic effects, closure of foetal ductus ateriosus in utero and possibly persistent pulmonary hypertension of newborn, kernicterus may occur in jaundiced neonates

Breastfeeding: Avoid—possible risk of Reye's syndrome; regular use of high doses could impair platelet function and produce hypoprothrombinaemia in neonate if neonatal vitamin K stores are low.

Adverse effects: Nausea, dyspepsia, GI ulceration or bleeding, tinnitus, vertigo, confusion, increased bleeding time. Hypersensitivity reactions including angioedema, bronchospasm and rash (including Stevens-Johnson syndrome [SJS]), iron deficiency anaemia, renal impairment, oesophageal ulceration, major haemorrhage (including GI, subconjunctival, or other), blood dyscrasias, oedema, myocarditis, Reye syndrome with subsequent encephalopathy and severe hepatic injury

Interactions with other medicines: Dexamethasone, enalapril, fluoxetine, heparin, hydrocortisone, ibuprofen, methotrexate, metoclopramide, phenytoin, prednisolone, spironolactone, valproic acid, warfarin

Notes

- Given with or after food.
- Acetylsalicylic acid should not be used in children who have or who are recovering from chickenpox (varicella), influenza, acute febrile illness or flu symptoms because of rare association with Reye's syndrome. During treatment with acetylsalicylic acid, changes in behavior may be an early sign of Reye's syndrome. Patients and caregivers should be instructed to contact the health care provider if these symptoms develop.

Celecoxib

ATC code: L01XX33

Capsules, 200 mg, LOU 4

Indications and dose

Adult

Pain and inflammation in osteoarthritis, oral: 200 mg daily in 1–2 divided doses, then increased if necessary up to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose

Pain and inflammation in rheumatoid arthritis, oral: 100 mg twice daily, then increased if necessary to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose

Ankylosing spondylitis, oral: 200 mg daily in 1–2 divided doses, then increased if necessary up to 400 mg daily in 1–2 divided doses, discontinue if no improvement after 2 weeks on maximum dose

Paediatrics: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications

- Active GI bleeding, active GI ulceration, cerebrovascular disease, inflammatory bowel disease, ischaemic heart disease, mild to severe heart failure, peripheral arterial disease, patients with sulphonamide sensitivity
- Allergy and cross-sensitivity: History of hypersensitivity to aspirin or any other NSAIM, which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAIM

Precautions: Allergic disorders, cardiac impairment (NSAIMs may impair renal function), coagulation defects, connective-tissue disorders, dehydration (risk of renal impairment), elderly (risk of serious adverse effects and fatalities), history of cardiac failure, history of GI disorders, hypertension, left ventricular dysfunction, oedema, risk factors for cardiovascular events

Hepatic impairment

- Manufacturer advises caution in mild to moderate impairment, avoid in severe impairment (no information available).
- Dose adjustments: Manufacturer advises initial dose reduction of 50% in moderate impairment.

Renal impairment

- Avoid if possible or use with caution.
- Avoid if estimated glomular filtration rate (eGFR) <30 mL/min/1.73 m2.
- Dose adjustments, the lowest effective dose should be used for the shortest possible duration.
- Monitor renal function; sodium and water retention may occur, and renal function may deteriorate, possibly leading to renal failure.

Conception and contraception: Caution—long-term use of some NSAIMs is associated with reduced female fertility, which is reversible on stopping treatment.

Pregnancy: Avoid (teratogenic in animal studies)

Breastfeeding: Avoid—present in milk in animal studies

Adverse effects: Angina pectoris, benign prostatic hyperplasia, cough, diarrhea, dizziness, dysphagia, dyspnea, fluid retention, GI discomfort, GI disorders, headache, hypersensitivity, hypertension, increased risk of infection, influenza like illness, injury, insomnia, irritable bowel syndrome, joint disorders, muscle tone increased, MI, nausea, nephrolithiasis, oedema, skin reactions, vomiting, weight increase, anaemia, anxiety, arrhythmias, breast tenderness, burping, cerebral infarction, chest pain, conjunctivitis, constipation, depression, drowsiness, dysphonia, electrolyte imbalance, embolism and thrombosis, fatigue, haemorrhage, hearing impairment, heart failure, hepatic disorders, lipoma, lower limb fracture, muscle complaints, nocturia, oral disorders, palpitations, paraesthesia, respiratory disorders, tinnitus, vision blurred, vitreous floater, acute kidney injury (more common in patients with pre-existing renal impairment), alopecia, angioedema, anosmia, ataxia, confusion, flushing, pain and inflammation in musculoskeletal disorders, hallucination, intracranial haemorrhage, leucopenia, meningitis aseptic, menstrual disorder, myositis, nephritis tubulointerstitial, nephropathy, pancreatitis, pancytopenia, photosensitivity reaction, seizures, severe cutaneous adverse reactions (SCARs), altered taste, thrombocytopenia, vasculitis

Interactions with other medicines: See Acetylsalicylic acid (Aspirin)

Notes: Dose adjustments due to interactions, reduce dose by half with concurrent use of fluconazole

Dexketoprofen

ATC code: M01AE17

Tablet, 25 mg, LOU 4

Injection, 25mg/ml (2ml amp), (as trometamol), LOU 5

Indications and dose

Adult

Short-term treatment of mild to moderate pain including dysmenorrhoea, musculo-skeletal pain, dental pain, post-operative pain, renal colic and low back pain, oral: 25 mg every 8 hours, maximum 75 mg per day. **Elderly:** Consider an initial maximum dosage of 50mg per day.

By IV or IM:

50 mg every 8-12 hours. If necessary, the administration can be repeated 6 hours apart. Maximum total daily dose should not exceed 150 mg. Treatment should be limited for acute symptomatic period (no more than 2 days). **Elderly:** No dosage adjustment is generally necessary. However, due to physiological decline in renal function in elderly patients a lower dose is recommended in case of mild renal function impairment: 50 mg total daily dose.

Paediatric:

No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Hypersensitivity to the active substance or to any of the excipients, children and adolescents, active bleeding or bleeding disorders, active or recurrent GI haemorrhage, active or recurrent GI ulcer, chronic dyspepsia, Crohn's disease, history of NSAIM-associated GI bleeding or perforation, known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates, severe dehydration, severe heart failure, ulcerative colitis, varicella infection, history of hypersensitivity to aspirin or any other NSAIM, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAIM

Cautions: Allergic disorders, asthma, cerebrovascular disease, coagulation defects, congenital disorder of porphyrin metabolism, congestive heart failure, dehydration, elderly (risk of serious adverse effects and fatalities), following major surgery, haematopoietic disorders, history of cardiac disease (NSAIMs may

cause fluid retention and oedema), history of GI disease, history of GI toxicity, ischaemic heart disease, mixed connective-tissue disorders, peripheral arterial disease, risk factors for cardiovascular events, SLE, uncontrolled hypertension

Hepatic impairment: Caution in mild to moderate impairment, avoid in severe impairment; dose adjustments - initial dose reduction to max. 50 mg daily in mild to moderate impairment.

Renal impairment:

- Avoid use if possible or use with caution as follows; dosage should be reduced to 50 mg total daily dose in patients with mildly impaired renal function (CrCl 50 - 80 mL/min).
- It should not be used in patients with moderate to severe renal dysfunction (CrCl <50 mL/min).
- Monitor renal function; sodium and water retention may occur, and renal function may deteriorate, possibly leading to renal failure.

Conception and contraception: Caution—long-term use of some NSAIMs is associated with reduced female fertility, which is reversible on stopping treatment.

Pregnancy: Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of foetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn), onset of labor may be delayed, and duration may be increased.

Breastfeeding: Use with caution.

Adverse effects: Diarrhoea, GI, discomfort, nausea, vomiting, anxiety, asthenia, chills, constipation, dizziness, drowsiness, dry mouth, flushing, GI disorders, headache, insomnia, malaise, pain, palpitations, skin reactions, vertigo, angioedema, appetite decreased, dyspnoea, haemorrhage, hepatic disorders, hyperhidrosis, hypersensitivity, hypertension, hypotension, menstrual disorder, nephritis, nephrotic syndrome, neutropenia, oedema, pancreatitis, paraesthesia, photosensitivity reaction, polyuria, prostatic disorder, respiratory disorders, SCARs, syncope, tachycardia, thrombocytopenia, tinnitus, vision blurred, acute kidney injury (more common in patients with pre-existing renal impairment), agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia, inflammatory bowel disease, meningitis aseptic oral ulceration, platelet aggregation inhibition, renal papillary necrosis.

Interactions with other medicines: Other NSAIMs (including cyclooxygenase-2 selective inhibitors) and high doses of salicylates (≥ 3 g/day), anticoagulants, corticosteroids, lithium, methotrexate, hydantoins, and sulphonamides.

Notes

- The lowest effective dose should be used for the shortest possible duration. Tablets are not intended for long-term use, and treatment must be limited to the symptomatic period.
- Tablet should be swallowed with a sufficient amount of fluid (e.g., one glass of water). Concomitant administration with food delays the absorption rate of the drug, thus, in case of acute pain, it is recommended that administration is at least 30 minutes before meals.
- In case of accidental or excessive intake, immediately institute symptomatic therapy according to the patient's clinical condition. Activated charcoal should be administered if more than 5 mg/kg has been ingested by an adult or a child within an hour.

Ibuprofen

ATC code: M01AE01

Tablet, 200 mg, LOU 2

Oral liquid, 100 mg/5 mL, LOU 2

Indications and dose

Pain and inflammation in rheumatic disease and other musculoskeletal disorders, including juvenile arthritis, mild to moderate pain, including dysmenorrhoea and headache, pain in children, acute migraine attack

Adult

Mild to moderate pain, pyrexia, inflammatory musculoskeletal disorders, oral: 1.2–1.8 g daily in 3–4 divided doses, increase if necessary to maximum 2.4 g daily (3.2 g daily in inflammatory disease), maintenance dose of 0.6–1.2 g daily may be sufficient

Paediatric

Mild to moderate pain, oral

Infant or **child over 3 months**: 5–10 mg/kg 3 or 4 times daily; maximum daily dose is 40 mg/kg/day

Juvenile arthritis, oral

Child over 7 kg: 30–40 mg/kg daily in 3–4 divided doses **Contraindications:** Hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAIM, active peptic ulceration or upper GI bleeding, severe renal failure, hepatic failure, or cardiac failure

Precautions: Asthma, cardiac disease, volume depletion, such as in gastroenteritis or dehydration (increased risk of renal impairment), concomitant use of drugs that increase risk of bleeding, previous peptic ulceration, coagulation defects, allergic disorders, renal impairment, hepatic impairment, cardiac disease, elderly, pregnancy, drug interactions

Hepatic impairment: Use with caution; increased risk of GI bleeding and can cause fluid retention; avoid in severe liver disease.

Renal impairment

- Mild: Monitor renal function; sodium and water retention may occur as may deterioration in renal function, possibly leading to renal failure.
- Moderate to severe: avoid

Adverse effects: GI disturbances including nausea, diarrhea, dyspepsia, ulceration, and hemorrhage, hypersensitivity reactions including rash, angioedema and bronchospasm, headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, tinnitus, photosensitivity, haematuria, fluid retention (rarely precipitating congestive heart failure in the elderly), raised blood pressure, renal failure, rarely hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme

(SJS), toxic dermal necrolysis (Lyell syndrome), colitis and aseptic meningitis

Interactions with other medicines (*indicates serious): *Acetylsalicylic acid, *ciclosporin, dexamethasone, digoxin, enalapril, *fluoxetine, furosemide, heparin, hydrocortisone, *levofloxacin, *lithium, *methotrexate, *ofloxacin, penicillamine, *phenytoin, prednisolone, propranolol, ritonavir, spironolactone, *warfarin, zidovudine

Notes: Given with or after food.

Ketorolac

ATC code: M01AB15

Injection,30 mg/mL, LOU 2

Indications and dose

Adult

Short-term management of moderate to severe acute post-operative pain only

Body weight up to 50 kg by IM or IV injection: Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days; frequency may be increased to up to every 2 hours during initial

Post-operative period, by IM or IV injection: Maximum 60 mg per day

Body weight 50 kg and above by IM or IV injection: Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days; frequency may be increased to up to every 2 hours during initial postoperative period, maximum 90 mg per day

- *Elderly by IM or IV injection*: Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days; frequency may be increased to up to every 2 hours during initial post-operative period, maximum 60 mg per day

Paediatric

Short-term management of moderate to severe acute post-operative pain only

IV or IM

Below 2 years: Safety and efficacy not established

2–16 years

Single dose: 0.5 mg/kg once; not to exceed 15 mg

Multiple dose: 0.5 mg/kg every 6hours; not to exceed 5 days

Over 16 years, <50 kg

IV: 15 mg as single dose or 15 mg every 6 hours; not to exceed 60 mg/day

IM: 30 mg as single dose or 15 mg every 6 hours; not to exceed 60 mg/day

Over 16 years, over 50 kg

IV: 30 mg as single dose or 30 mg every 6 hours; not to exceed 120 mg/day

IM: 60 mg as single dose or 30 mg every 6 hours; not to exceed 120 mg/day.

Contraindications: Active or history of GI bleeding, active or history of GI ulceration, coagulation disorders, complete or partial syndrome of nasal polyps, confirmed or suspected cerebrovascular bleeding, dehydration, following operations with high risk of haemorrhage or incomplete haemostasis, haemorrhagic diatheses, history of GI bleeding related to previous NSAIM therapy, history of GI perforation related to previous NSAIM therapy, hypovolaemia, severe heart failure. Allergy and cross-sensitivity contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAIM, which includes those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAIM.

Precautions: Allergic disorders, cardiac impairment (NSAIMs may impair renal function), cerebrovascular disease, connective-tissue disorders, elderly (risk of serious adverse effects and fatalities), heart failure, history of GI disorders (e.g., ulcerative colitis, Crohn's disease), ischaemic heart disease, peripheral arterial disease, risk factors for cardiovascular events, uncontrolled hypertension

Renal impairment

- Severe: Contraindicated
- Moderate (moderately elevated serum creatinine): Use 50% of recommended dosage, not to exceed 60 mg/day IM/IV

Hepatic impairment: Not studied, use caution, discontinue if symptoms of liver toxicity develop

Adverse effects: Agranulocytosis, angioedema, anxiety, aplastic anaemia, appetite decreased, asthenia, asthma, azotaemia, bradycardia, burping, chest pain, concentration impaired, confusion, constipation, Crohn's disease aggravated, depression, diarrhoea, dizziness, drowsiness, dry mouth, dyspnea, electrolyte imbalance, embolism and thrombosis, euphoric mood, fever, flank pain, fluid retention, flushing, GI discomfort, GI disorders, haemolytic anaemia, haemorrhage, hallucination, headache, hearing loss, heart failure, hepatic disorders, hyperhidrosis, hyperkinesia, hypersensitivity, hypertension, hypotension, infertility female, malaise, meningitis aseptic (patients with connective-tissue disorders such as SLE may be especially susceptible), musculoskeletal disorder, myalgia, MI, nausea, nephritis tubulointerstitial, nephropathy, neutropenia, oedema, optic neuritis, oral disorders, pallor, palpitations, pancreatitis, paraesthesia, perforation, photosensitivity reaction, platelet aggregation inhibition, psychotic disorder, pulmonary oedema, renal impairment, respiratory disorders, seizure, SCARs, skin reactions, sleep disorders, stroke, taste altered, thinking abnormal, thirst, thrombocytopenia, tinnitus, ulcer, urinary disorders, vertigo, visual impairment, vomiting, weight increased, wound haemorrhage

Interactions: See Acetylsalicylic Acid (Aspirin)

Notes

- Use for acute pain <5 days.
- Conception and contraception: Caution—long-term use of some NSAIMs is associated with reduced female fertility, which is reversible on stopping treatment.

Paracetamol

ATC code: N02BE01

Injection, 10 mg/mL (100 mL), LOU 4

Oral liquid, 120 mg/5 mL, LOU 1

Suppository, 125 mg, LOU 2

Tablet, 500 mg (scored), LOU 1

Indications and dose

Mild to moderate pain, including dysmenorrhoea and headache, pain relief in osteoarthritis and soft tissue lesions, pyrexia, including post-immunization pyrexia, acute migraine attack

Adult

Mild to moderate pain, pyrexia, oral: 0.5–1 g every 4–6 hours, maximum 4 g daily

By IV infusion

Body weight up to 50 kg: 15 mg/kg every 4–6 hours; dose to be administered over 15 minutes; maximum 60 mg/kg per day

Body weight 50 kg and above: 1 g every 4–6 hours, dose to be administered over 15 minutes; maximum 4 g per day

By rectum: 0.5–1 g

Mild to moderate pain or pyrexia in patients with risk factors for hepatotoxicity by IV infusion

Body weight up to 50 kg: 15 mg/kg every 4–6 hours, dose to be administered over 15 minutes, maximum 60 mg/kg per day

Body weight 50 kg and above: 1 g every 4–6 hours; dose to be administered over 15 minutes; maximum 3 g per day

Paediatric

Mild to moderate pain, fever, oral

Child 3–5 months: 60 mg every 4–6 hours, maximum 4 doses per day

Child 6–23 months: 120 mg every 4–6 hours, maximum4 doses per day

Child 2–3 years: 180 mg every 4–6 hours, maximum4 doses per day

Child 4–5 years: 240 mg every 4–6 hours, maximum4 doses per day

Child 6–7 years: 240–250 mg every 4–6 hours, maximum 4 doses per day

Child 8–9 years: 360–375 mg every 4–6 hours, maximum 4 doses per day

Child 10–11 years: 480–500 mg every 4–6 hours, maximum 4 doses per day

Child 12–15 years: 480–750 mg every 4–6 hours, maximum 4 doses per day

Child 16–17 years: 0.5–1 g every 4–6 hours, maximum 4 doses per day

Mild to moderate pain, fever, by rectum

Child 3–11 months: 60–125 mg every 4–6 hours as required, maximum 4 doses per day

Child 1–4 years: 125–250 mg every 4–6 hours as required, maximum 4 doses per day

Child 5–11 years: 250–500 mg every 4–6 hours as required, maximum 4 doses per day

Child 12–17 years: 500 mg every 4–6 hours

Post-immunisation fever in infants, oral

Child 2–3 months: 60 mg for 1 dose, then 60 mg after 4–6 hours if required

Child 4 months: 60 mg for 1 dose, then 60 mg after 4–6 hours, maximum 4 doses per day.

Precautions: Hepatic impairment, alcohol dependence, over dosage, malnutrition

Hepatic impairment: Dose related toxicity, avoid large doses.

Renal impairment: Infusion dose interval is increased to every 6 hours if eGFR is < 30 mL/min/1.73 m2

Pregnancy and breastfeeding: Not known to be harmful

Adverse effects

- Rare: Rash, hypersensitivity, blood disorders including neutropenia, thrombocytopenia, pancytopenia.
- Hepatotoxicity (and less frequently renal damage) can occur after paracetamol overdosage.
- Children in the following situations may be at an increased risk of liver damage from paracetamol overdosage: Malnourished, obese, febrile illness, prolonged course, not eaten for a few days or taking liver enzyme inducing drugs.

Interactions with other medicines: Metoclopramide, warfarin

Notes

- The suspension should be shaken well before use.
- Infants under 3 months should not be given paracetamol unless advised by a doctor; a dose of 10 mg/kg (5 mg/kg if jaundiced) is suitable.
- Not recommended for anti-inflammatory use because of lack of proven benefit.

3.2. Opioid Analgesics

Opioid Conversion Table

No.	Opioid	mg per day	Morphine Equivalent Dose
1	Fentanyl Transdermal (in microgram/hr)	1	2.4
2	Methadone	1	3
3	Oxycodone	1	1.5
4	Tramadol	1	0.1
5	Dihydrocoeine Phosphate	1	0.1

Dihydrocodeine

ATC code: N02AA08

Tablet, 30 mg (phosphate), LOU 4

Indications and dose: Mild to moderate pain

Adult

Mild to moderate pain, oral: 30–60 mg every 4 hours when necessary; maximum 240 mg daily

Chronic severe pain, oral using modified-release medicines: 60–120 mg every 12 hours

Severe pain, oral: 40–80 mg 3 times a day; maximum 240 mg per day

Paediatric

Child 1–12 years: 0.5–1 mg/kg every 4–6 hours when needed; maximum, 240 mg daily

Contraindications: Respiratory depression, obstructive airways disease, acute asthma attack, where risk of paralytic ileus is present, children under 1 year old, productive cough, elderly, head injury, acute alcoholism, heart failure secondary to chronic lung disease

Precautions: Pancreatitis, renal impairment and hepatic impairment, dependence, pregnancy, and breastfeeding, overdosage

Hepatic impairment

» Caution, consider avoiding.

» Dose adjustments: Manufacturer advises dose reduction, if used.

Renal impairment: Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs

Breastfeeding: Use only if potential benefit outweighs risk.

Interactions with other medicines: Alcohol, CNS depressants, buprenorpine, MAOIs, naltrexone, antidiarrhoeal agents

Adverse effects: Constipation particularly troublesome in long-term use, dizziness, nausea, vomiting, difficulty with micturition, ureteric or biliary spasm, dry mouth, headaches, sweating, facial flushing, in therapeutic doses, codeine is much less liable than morphine to produce tolerance, dependence, euphoria, sedation, or other adverse effects, Dysuria, mood altered, With oral use Biliary spasm, bronchospasm, hypothermia, sexual dysfunction, ureteral spasm

Fentanyl

ATC code: N02AB03

Transdermal patch, 25 micrograms/hour, LOU 5

Transdermal patch, 50 micrograms/hour, LOU 5

Indications and dose

Adult

Chronic intractable pain not currently treated with a strong opioid analgesic by transdermal application: Initially 12 micrograms/hour every 72 hours; alternatively initially 25 micrograms/hour every 72 hours; when starting, evaluation of the analgesic effect should not be made before the system has been worn for 24 hours (to allow for the gradual increase in plasma-fentanyl concentration)—previous analgesic therapy should be phased out gradually from time of first patch application; dose should be adjusted at 48–72 hour intervals in steps of 12–25 micrograms/hour; if necessary, more than one patch may be used at a time (but applied at the same time to avoid confusion)—consider additional or alternative analgesic therapy if dose required exceeds 300 micrograms/hour (**Important**: It takes 17 hours or more for the plasma-fentanyl concentration to decrease by 50%—replacement opioid therapy should be initiated at a low dose and increased gradually.)

Chronic intractable pain currently treated with a strong opioid analgesic by transdermal application: Initial dose based on previous 24-hour opioid requirement (consult product literature); for evaluating analgesic efficacy and dose increments, see chronic intractable pain not currently treated with a strong opioid analgesic; for conversion from long-term oral morphine to transdermal fentanyl, see pain management with opioids under prescribing in palliative

Paediatric

Chronic intractable pain not currently treated with a strong opioid analgesic by transdermal application

Child 2–17 years: Initial dose based on previous 24-hour opioid requirement (consult product literature); for evaluating analgesic efficacy and dose increments, see chronic intractable pain not currently treated with a strong opioid analgesic; for conversion from long-term oral morphine to transdermal fentanyl

Child 16–17 years: Initially 12 micrograms/hour every 72 hours; alternatively initially 25 micrograms/hour every 72 hours; when starting, evaluation of the analgesic effect should not be made before the system has been worn for 24 hours (to allow for gradual increase in plasma-fentanyl concentration)—previous analgesic therapy should be phased out gradually from time of first patch application; dose should be adjusted at 48–72 hour intervals in steps of 12–25 micrograms/hour; if necessary, more than one patch may be used at a time (but applied at the same time to avoid confusion)—consider additional or alternative analgesic therapy if dose required exceeds 300 micrograms/hour (Important: It takes 17 hours or more for the plasma-fentanyl concentration to decrease by 50%—replacement opioid therapy should be initiated at a low dose and increased gradually.)

Precautions: Cerebral tumour, diabetes mellitus, impaired consciousness

Hepatic impairment

» Manufacturer advises caution (risk of accumulation).

» Dose adjustments: Manufacturer advises cautious dose titration.

Renal impairment: Avoid use or reduce dose, opioid effects increased, and prolonged and increased cerebral sensitivity occurs.

Breastfeeding: With transdermal use, manufacturer advises avoiding during treatment and for 72 hours after removal of patch—present in milk.

Adverse reactions: With transdermal use anxiety, appetite decreased, asthenia, depression, diarrhea, dyspnea, GI discomfort, hypertension, insomnia, malaise, muscle complaints, peripheral oedema, sensation abnormal, temperature sensation altered, tremor Consciousness impaired, cyanosis, fever, GI disorders, influenza like illness, memory loss, respiratory disorders, seizures, sexual dysfunction, vision blurred Apnoea

Interactions with other medicines: Azole antifungals, CCBs, HIV protease inhibitors, macrolide antibiotics, rifamycins, carbamazepine, phenytoin, and MAOIs

Notes

- **Directions for administration:** With transdermal use for patches, apply to dry, non-irritated, non-irradiated, non-hairy skin on torso or upper arm, removing after 72 hours and siting replacement patches on a different area (avoid using the same area for several days) because sensitivity occurs
- Transdermal fentanyl patches are not suitable for acute pain or for those patients whose analgesic requirements are changing rapidly because the long time to steady-state prevents rapid titration of the dose. Risk of fatal respiratory depression, particularly in patients not previously treated with a strong opioid analgesic: Manufacturer recommends use only in opioid-tolerant patients.

Methadone

ATC code: N07BC02

Oral liquid, 1mg/mL (as HCL), LOU 4

Tablet, 5mg, LOU 4

Indication and dose

Adult

Management of severe pain, for long term opioid treatment where alternative treatments are inadequate and as an adjunct in treatment of opioid dependence (prescribed under specialist palliative supervision), *oral:* 5–10 mg every 8 hours, adjusted according to response, on prolonged use not to be given more frequently than every 12 hours. Note: Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

For treatment of opioid dependence: see section 25.5 Medicines for Disorders due to Psychoactive Substance Abuse.

Paediatric: Not recommended (see also under Precautions)

Contraindications, Precautions, Adverse effects, and Interactions: *See section 25.5 Medicines for Disorders due to Psychoactive Substance Abuse.*

Notes:

- Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory.
- Do not abruptly discontinue Methadone tablets in a physically dependent patient.
- The final strength of the methadone mixture to be dispensed to the patient should be specified on the prescription (care over concentrate strengths used for opioid dependence and lower strength for palliative pain). Care is required in prescribing and dispensing the correct strength because any confusion could lead to an overdose.

Morphine

ATC code: N02AA01

Injection, 10 mg (as HCl or sulphate)/1-mL amp, LOU 4

Injection (for infusion): 30 mg/mL, LOU 4

Oral liquid, 1 mg (as HCl or sulphate)/mL, LOU 3

Oral liquid, 10 mg (as HCl or sulphate)/mL, LOU 3

Tablet (m/r), 30 mg (sulphate) morphine, LOU 4

Indications and dose:

Post-operative pain, severe acute, and chronic pain; opioids should be used in a multimodal plan with other analgesics (paracetamol, NSAIMs, anaesthetic blocks) for opioid dose sparing.

Adult

Acute pain by SC injection (not suitable for edematous patients) or by IM injection: 0.1 mg/kg every 4 hours if necessary

Chronic pain, oral (immediate-release tablets) or by SC injection (not suitable for edematous patients) or by IM injection: 5–20 mg regularly every 4 hours, dose may be increased according to need.

Note: Oral dose should be approximately double corresponding SC dose, titrate dose first using immediate-release oral preparation, then convert dose to every 12 hours; according to daily morphine requirement (using oral sustained-release tablets).

Control of severe acute pain, by IV injection: Titration of 1 mg (or 0.01 mg/kg) every 10 min, till analgesia is achieved

MI by slow IV injection (2 mg/min): 10 mg followed by a further 5–10 mg if necessary

- **Elderly or debilitated patients:** Reduce dose by half.

Acute pulmonary edema by slow IV injection (2 mg/min): 5–10 mg

Paediatric

Pain, SC, or IM

Neonate: 100 micrograms/kg every 6 hours, adjusted according to response

Infant 1–6 months: Initially 100–200 micrograms/kg every 6 hours, adjusted according to response

Infant or **child 6 months–2 years**: Initially 100–200 micrograms/kg every 4 hours, adjusted according to response

Child 2–12 years: Initially 200 micrograms/kg every 4 hours, adjusted according to response; usual maximum dose is 15 mg.

Pain, IV injection over at least 5 minutes:

Neonate: Initially 50 micrograms/kg every 6 hours, adjusted according to response

Infant 1–6 months: Initially 100 micrograms/kg every 6 hours, adjusted according to response

Infant or **child 6 months–12 years:** Initially 100 micrograms/kg every 4 hours, adjusted according to response; maximum dose is 15 mg

Pain, IV injection and infusion

Neonate: Initially by IV injection (over at least 5 minutes) 25–100 micrograms/kg then by continuous IV infusion 5–40 micrograms/kg/hour adjusted according to response

Child 1–6 months: Initially by IV injection (over at least 5 minutes) 100–200 micrograms/kg then by continuous infusion 10–30 micrograms/kg/hour adjusted to response

Child 6 months–12 years: Initially by IV injection (over at least 5 minutes) 100–200 micrograms/kg then by continuous IV infusion 20–30 micrograms/kg/hour adjusted according to response.

Pain, oral

Child 1–12 months: Initially 80–200 micrograms/kg every 4 hours, adjusted according to response

Child 1–2 years: Initially 200–400 micrograms/kg every 4 hours, adjusted according to response

Child 2–12 years: Initially 200–500 micrograms/kg (maximum 20 mg) every 4 hours, adjusted according to response

Pain, oral (prolonged release)

Child: Initially 200–800 micrograms/kg every 12 hours, adjusted according to response

Pain, continuous SC infusion

Child 1–3 months: 10 micrograms/kg/hour

Child 3 months–18 years: 20 micrograms/kg/hour

Notes:

For neonatal intensive care infusions, dilute 2.5 mg/kg body weight to a final volume of 50 mL with infusion fluid.

Extreme caution should be exercised in determining all drug doses in children. There is a risk of misplacing the decimal point with morphine, resulting in a 10 times overdose.

Contraindications: Respiratory depression, severe respiratory disease, CNS depression, risk of paralytic ileus, raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma

Precautions

- Renal impairment, hepatic impairment, dependence (severe withdrawal symptoms if withdrawn abruptly), hypothyroidism, convulsive disorders, decreased respiratory reserve and acute asthma, hypotension, prostatic hypertrophy, overdosage
- Skilled tasks: Warn patient or caregiver about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike or operating machinery, for 24 hours.

Renal impairment

- Mild to moderate: Reduce dose by 25%
- Severe: Reduce dose by 50% or avoid

Hepatic impairment: Avoid or reduce dose, may precipitate coma

Adverse reactions: Nausea, vomiting, constipation, lightheadedness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, anorexia, spasm of urinary and biliary tract, pruritus, rash, sweating, postural hypotension, miosis, respiratory depression (dose related), bradycardia, tachycardia, palpitations, SIADH, anaphylaxis

Interactions with other medicines (*indicates serious): Amitriptyline, chlorpromazine, ciprofloxacin, diazepam, haloperidol, metoclopramide, *ritonavir

Notes

- Patients on opioid analgesics must, at the start of therapy, be closely monitored for severe adverse effects, opioid induced ventilatory impairment. This presents initially as increasing sedation before progressing to respiratory arrest. Therefore, these patients must be monitored for increasing sedation (drowsiness) and interventions offered (from dose reduction to naloxone administration). Normal sleep must be differentiated from opioid-induced sedation, especially at night.
- Co-prescribe laxatives and anti-emetics to preempt constipation, nausea, and vomiting.
- Opioid analgesics are not recommended for managing chronic non-cancer pain (e.g., chronic non-specific low back pain, chronic visceral pain).
- SC injection is not suitable for edematous patients. Administer IV injection slowly over 5 minutes.
- For continuous IV infusion, dilute with glucose 5% or 10% or sodium chloride 0.9%.
- Prolonged release morphine preparations must not be crushed or chewed. Child must be able to swallow the tablet whole.
- Doses should be adjusted according to response.

Oxycodone

ATC code: N02AA05

Tablet (immediate-release), 5mg (as HCL), LOU 6

Indications and dose

Adult

Severe acute pain such as post-operative pain, chronic pain such as palliative care, intermittent or breakthrough pain, oral: Initially 5mg every 4-6 hours, dose to be increased if necessary, according to severity of pain. Maximum 400mg per day. **Elderly:** Reduce the starting dose to one-third to one-half as per the indication and titrate the dose cautiously.

Paediatric:

Not licensed for use in children under 12 years and some preparations may not be licensed for use in children—further information can be found in the product literature of the individual preparations.

Moderate to severe pain in palliative care, oral:

Child 12–17 years: Initially 5 mg every 4-6 hours, dose to be increased if necessary, according to severity of pain.

Contraindications: Hypersensitivity to the active substance or to any of the excipients, alvimopan use, Respiratory depression, severe respiratory disease, CNS depression, risk of paralytic ileus, raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma

Precautions: Restlessness, Sedation, Seizures, Severe cardiac arrhythmias, Shock, ST-segment elevation, Sweating, flushing, warmness of face/neck/upper thorax, Urinary retention, oliguria, Ventricular tachycardia, Visual disturbances, Vomiting, Weakness, Agitation, Angina pectoris, Anticholinergic effects (dry mouth, palpitation, tachycardia), Bradycardia, Cardiac arrest, Coma, Constipation, Dizziness, Dysphoria, Euphoria, Faintness, Mental clouding/depression, Myocardial infarction, Nausea, Nervousness, Pruritus, urticarial, QT-interval prolongation, Respiratory arrest, Respiratory/circulatory depression.

Hepatic impairment: Reduce dose in cases of severe impairment.

Renal impairment: Dose reduction is required for end stage renal impairment due to a prolonged elimination half-life**.**

Pregnancy: Prolonged use during pregnancy can cause neonatal opioid withdrawal syndrome

Labour and delivery: Oxycodone crossed the placental barrio and may cause respiratory depression and psycho-physiologic effects in neonates. If given during labour it may cause reduced duration, strength and frequency of uterine contractions leading to prolonged labour, however in some instances it may cause increased rate of cervical dilatation leading to shortened labour.

Fertility: Prolonged use of oxycodone may cause reduced fertility due to androgen deficiency.

Breastfeeding: Excreted in breast milk therefore the developmental health needs of the newborn should be considered and weighed against the mother's clinical needs for therapy.

When used in breastfeeding mothers, monitor the infant for excess sedation and respiratory depression. Withdrawal syndromes may be observed in breastfed infants when administration of oxycodone is stopped, or breastfeeding is stopped.

Adverse effects: Nausea, vomiting, constipation, lightheadedness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, anorexia, spasm of urinary and biliary tract, pruritus, rash, postural hypotension, miosis, respiratory/circulatory depression (dose related), bradycardia, tachycardia, palpitations, syndrome of inappropriate antidiuretic hormone secretion (SIADH), anaphylaxis.

Interactions with other medicines (*indicates serious): *grape fruit, *amobabital, *atemether / lumefantrine,*asenapine,*atazanavir,*avaoritini, *benzhydrocodone/acetaminophen, *brivaracetamcalcium/magnesium/ sodiumoxybate/potassium, *cimetidine, *clonidine,*conivaptan,*diazepam intranasal, *fentanyi, *fluoxetine, *hydrocodone, *isoniazid, *linezolide, *lopinavir, *methyl blue,*nelfinavir, *quinidine,*ritonavir, *saquinavir, *selegiline,*tramadol *quinidine, Alprazolum, amiodarone, amitriptyline, atracurium, baclophen, buprenorphine, caffeine, carbamazepine, celecoxi, chloramphenicol,cimetidine, clomipramine, clonazepam, codeine,c yclizine, duranavir, desipramine, diazepam, dihydrocodeine, dopamine, efivarenz, ephedrine, ehanol, etomidate, fluphenazine, gabapentinhalopridol, itraconazole, ketoconazole, levoconazole, marijuana, midazolam, mifeprisol, morphine, olanzapine, oxymophone, pancuronium, phenobarbital, pregabalin, propofol, promethazine, selegiline,tabutaline, tramadol

Notes:

» Dose modification: adjust the dose to a third (1/3) to half (1/2) the recommended starting dose if being co-administered with other CNS depressants. Monitor for sedation respiratory depression and hypotension.

Tramadol

ATC Code N02AX02

Capsule, 50mg, LOU 5

Injection, 50mg/mL, (2mL Ampoule), LOU 5

Indications and dose

Tramadol is an atypical opioid, useful for management of moderate to severe pain where alternative therapies are inadequate. Useful for mixed pain- neuropathic and nociceptive.

Adult

By oral:

Acute pain, oral: 50-100mg every 4-6 hours when required, do not exceed 400mg in 24 hours.

Chronic pain, oral: Initially 25mg, titrate upwards by 25-50mg every 3 days up to 50-100mg every 4-6 hours when required, do not exceed 400mg in 24 hours.

By IM, bolus, slow IV or SC:

Moderate to severe pain, by IM, bolus, slow IV or SC: 50-100mg every 4-6hrs, for slow IV give over 2-3 minutes.

Moderate to severe acute pain by IM, bolus, slow IV or SC: 100mg initially, then50–100mg every 4–6hours; do not exceed 400mg in 24 hours.

Moderate to severe chronic pain by IM, bolus, slow IV or SC: Initially 50mg then adjust the dose according to the patient's response. Do not exceed 400mg in 24 hours.

Postoperative pain, by IM, bolus, slow IV or SC: Initially 100mg (in the first hour), then 50mg every 10-20 minutes if required up to 250mg (including the initial dose). Maintenance dose: 50-100mg every 4-6 hours. For IV give over 2-3 minutes. Do not exceed

400mg in 24 hours.

Elderly >65 years: give the initial dose at the lower end of dosing range. Do not to exceed 300 mg in 24 hours if >75 years. Titrate doses cautiously.

Paediatric:

Children 1 month to 11 years: Safety and efficacy is not established with Life-threatening respiratory depression and death have occurred on receiving tramadol.

By oral:

Moderate to severe acute pain, oral:

Child 12–17 years: Initially 100mg, then 50–100mg every 4–6 hours; do not exceed 400mg in 24 hours.

Moderate to severe chronic pain, oral:

Child 12–17 years: Initially 50 mg, then, adjusted according to response; maximum 400 mg in 24 hours.

By IM, slow IV (over 2-3 mins), IV infusion, or SC:

Moderate to severe acute pain, by IM, IV, IV infusion, or SC:

Child 12–17 years: 50–100mg every 4-6hours; do not exceed 400mg in 24 hours. IV injection to be given over 2-3 minutes.

Postoperative pain, by slow IV (over 2-3 mins), IM, IV infusion or SC:

Child 12–17 years: Initially 100 mg, then 50 mg every 10–20 minutes if required up to total maximum 250mg (including initial dose) in first hour, then 50–100 mg every 4–6 hours; Maximum 400 mg in 24 hours.

Contraindications: Hypersensitivity to the active substance or to any of the excipients, acute intoxication with alcohol, acute intoxication with analgesics, acute intoxication with hypnotics, acute intoxication with opioids, uncontrolled epilepsy, known or suspected gastrointestinal obstruction, including paralytic ileus, Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within last 14 days, Children <12 years, Postoperative management in children <18 years following tonsillectomy and/or adenoidectomy, Severe/acute bronchial asthma in an unmonitored setting or in absence of resuscitative equipment, Significant respiratory depression

Precautions: Excessive bronchial secretions, history of epilepsy—use tramadol only if compelling reasons, impaired consciousness, not suitable as a substitute in opioid-dependent patients, not suitable in some types of general anaesthesia, postoperative use, susceptibility to seizures—use tramadol only if compelling reasons, variation in metabolism

Renal impairment:

- For patients with CrCl of ≥30 mL/minute: No dosage adjustments necessary, exercise caution during use.
- For patients with severe renal impairment (CrCl <30 mL/min): Oral dose as 50-100 mg every 12 hours
- For patients on dialysis: May receive regular dose on dialysis days; only 7% of dose is removed by hemodialysis

Hepatic impairment: For patients with mild-to-moderate hepatic impairment: No dosage adjustments necessary; use with caution. In Severe hepatic impairment: Dose oral as 50mg every 12 hours.

Pregnancy: Prolonged use during pregnancy can cause neonatal opioid withdrawal syndrome

Labour and delivery: Use is not recommended in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Tramadol crossed the placental barrio and may cause respiratory depression and psycho-physiologic effects in neonates.

Breastfeeding: Tramadol and its active metabolite, O-desmethyltramadol (M1), are present in human milk. Published studies and cases reported excessive sedation, respiratory depression, and death in infants exposed to codeine via breast milk. Some women metabolize tramadol to M1 faster, this may lead to higher serum levels which may increase the risk in breastfeeding infants.

Adverse effects: allergic reaction, anaphylaxis, death, suicidal tendency, weight loss, Serotonin syndrome, Orthostatic hypotension, syncope, tachycardia. Central Nervous System: Abnormal gait, amnesia, cognitive dysfunction, depression, difficulty in concentration, hallucinations, paresthesia, seizure, tremor, Dyspnea, Stevens Johnson syndrome, toxic epidermal necrolysis, urticaria, vesicles, Dysgeusia, Dysuria, menstrual disorder

Interactions with other medicines (*indicates serious): Contraindicated with use with: Alvimopan, procarbazine, rasagiline, safinamide, and selegiline. *Acrivastine, *alfentanil, *amisulpride, *apalutamide, *asenapine transdermal, *belladonna, *opium, *benzhydrocodone/acetaminophen, *bremelanotide, *buprenorphine (including buccal, subdermal implant, transdermal, and long-acting injections preparations), *butorphanol, *calcium/magnesium/potassium/sodium oxybates, *clonidine, *codeine, *cyclobenzaprine, *dacomitinib, *desvenlafaxine, *dextromoramide, *diamorphine, *diazepam intranasal, *difenoxin hcl, *diphenoxylate HCl, *dipipanone, *duloxetine, *eluxadoline, *fentanyl, *givosiran, *hydrocodone, *linezolid, *methadone, *methylene blue, *metoclopramide intranasal, *morphine, *oxycodone, *selegiline transdermal, 5-HTP, cimetidine, diazepam, erythromycin

Notes:

- Tramadol is not suitable for narcotic withdrawal treatment.

3.3. Adjuncts For Pain Management & Medicines For Other Symptoms In Palliative Care

Amitriptyline

ATC code: N06AA09

Tablet, 25 mg, LOU 2

Indications and dose

Neuropathic pain in palliative care, depression

Adult

Depression, oral: Initially 75 mg daily (25–75 mg, daily in the elderly and adolescents) in divided doses or as a single dose at bedtime, increased gradually to 150–200 mg daily as necessary.

Neuropathic pain: Migraine prophylaxis, chronic tension type headache prophylaxis; oral, initially 10–25 mg daily, taken in the evening, then increased, if tolerated, in steps of 10–25 mg every 3–7 days in 1–2 divided doses; usual dose 25–75 mg daily, taken in the evening; doses above 100 mg should be used with caution (doses above 75 mg should be used with caution in the elderly and in patients with cardiovascular disease), maximum per dose 75 mg

Paediatric

Neuropathic pain, oral

Child 2–12 years: Initially 200–500 micrograms/kg (maximum 25 mg) once daily at night, increased if necessary to a maximum of 1 mg/kg twice daily.

Contraindications: Recent MI, arrhythmias (especially heart block), manic phase in bipolar disorders, severe liver disease, porphyria

Precautions

- History of epilepsy, hepatic impairment, thyroid disease, phaeochromocytoma, history of mania, psychoses, or depression (may aggravate psychotic or depressive symptoms), angle closure glaucoma, history of urinary retention, concurrent electroconvulsive therapy
- Avoid abrupt withdrawal, anaesthesia (increased risk of arrhythmias and hypotension)
- Skilled tasks: Warn patient or caregiver about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike or operating machinery, for 24 hours.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Sedative effects increased (avoid in severe liver disease).

Adverse reactions

- Sedation, dry mouth, blurred vision (disturbance of accommodation, increased intraocular pressure), constipation, nausea, difficulty in micturition, cardiovascular adverse effects particularly with high dosage including electrocardiogram (ECG) changes, arrhythmias, postural hypotension, tachycardia, syncope, sweating, tremor, rash and hypersensitivity reactions (urticaria, photosensitivity), behavioral disturbances, hypomania or mania, confusion or delirium, headache, interference with sexual function, blood sugar changes, increased appetite and weight gain (occasional weight loss), endocrine adverse effects such as testicular enlargement, gynaecomastia and galactorrhoea, movement disorders and dyskinesias, dysarthria, paraesthesia, taste disturbances, tinnitus, fever, abnormal liver function tests, blood dyscrasias including agranulocytosis, leukopenia, eosinophilia, purpura and thrombocytopenia, hepatitis, paralytic ileus, SIADH with hyponatraemia, seizures, prolonged QT interval.
- In overdose (high rate of fatality), excitement, restlessness, marked anticholinergic effects, severe symptoms including unconsciousness, convulsions, myoclonus, hyper-reflexia, hypotension, acidosis, respiratory and cardiac depression with arrhythmias

Interactions with other medicines (*indicates serious): *Alcohol, *atemether + lumefantrine, atropine, *carbamazepine, chlorpheniramine, *chlorpromazine, codeine, contraceptives (oral), diazepam, *epinephrine, *ethosuximide, *fluphenazine, furosemide, haloperidol, halothane, hydrochlorothiazide, isoniazid, ketamine, levothyroxine, morphine, nitrous oxide, *phenobarbital, *phenytoin, rifampicin, *ritonavir, spironolactone, thiopental, *valproic acid, *warfarin

Bisacodyl

ATC code: A06AB02

Tablet, 5 mg, LOU 2

Indications and dose

Adult

Constipation, oral: 5–10 mg once daily, increased if necessary up to 20 mg once daily, taken at night

Bowel clearance before radiological procedures and surgery, oral: Initially, 10 mg twice daily, dose to be taken in the morning and evening on the day before procedure

Paediatric

Constipation, oral

Child 4–17 years: 5–20 mg once daily, adjusted according to response, taken at night

Contraindications: Acute abdominal conditions, acute inflammatory bowel disease, intestinal obstruction, severe dehydration

Precautions: Excessive use of stimulant laxatives can cause diarrhea and related effects such as hypokalaemia; prolonged use may harm intestinal function; risk of electrolyte imbalance with prolonged use

Pregnancy: May be suitable for constipation in pregnancy if a stimulant effect is necessary.

Adverse effects: GI discomfort, nausea, haematochezia, vomiting, angioedema, colitis, dehydration

Notes

- Pharmacokinetics: Tablets work in 10–12 hours, suppositories work in 20–60 minutes unlicensed use
- Paediatric higher dose option is not licensed.

Carbamazepine

ATC code: N03AF01

Tablet (scored), 200 mg, LOU 4

Indications and dose

Adult

Trigeminal neuralgia, oral: Initially 100 mg 1–2 times a day, increased gradually according to response; usual dose 200 mg 3–4 times daily (up to 1.6 g daily may be needed in some patients)

Paediatric

Not licensed for use in Trigeminal neuralgia in children. Consult a specialist.

Contraindications, Precautions, Pregnancy, Breastfeeding, Adverse effects, Interactions with other medicines and Notes: *See section 6: Anticonvulsants and Antiepileptics*

Dexamethasone

ATC code: H02AB02

Injection, 4 mg (as sodium phosphate)/1-mL amp, LOU 3

Tablet, 500 micrograms, LOU 3

Tablet (scored), 4 mg, LOU 3

Indications and dose

Adjunct in the emergency treatment of anaphylaxis, short-term suppression of inflammation in allergic disorders.

Adult

Allergy (short-term use), oral: Usual range 0.5–10 mg daily as a single dose in the morning

Anaphylaxis (adjunct), by slow IV injection or infusion (as dexamethasone phosphate): 0.5–24 mg

Paediatric

Inflammatory and allergic disorders, IM or slow IV injection or infusion

Infant or **Child** 100–400 micrograms/kg in 1–2 divided doses (maximum 24 mg daily)

Contraindications: Not relevant to emergency use

Precautions: Increased susceptibility to and severity of infection, activation or exacerbation of TB, amoebiasis, strongyloidiasis, risk of severe chickenpox in non-immune patients (varicella zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus, peptic ulcer, hypertension, corneal perforation, osteoporosis, myasthenia gravis

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects

- Incidence of adverse effects is related to dose and duration of treatment.
- Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.
- Common: Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects, with IV use: transient itching, burning, or tingling in perineal area (after IV bolus)
- Rare: Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions, including anaphylaxis
- Psychiatric: Include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behavior, delirium or psychosis is less common

Interactions with other medicines (*indicates serious): Acetylsalicylic acid, albendazole, *amphotericin B, *carbamazepine, contraceptives (oral), digoxin, enalapril, erythromycin, furosemide, hydrochlorothiazide, ibuprofen, insulins, *lopinavir, metformin, *methotrexate, *phenobarbital, *phenytoin, praziquantel, propranolol, *rifampicin, ritonavir, salbutamol, saquinavir, spironolactone, infuenza vaccine, *live vaccines, *warfarin

Diazepam

ATC code: N05BA01

Injection, 5 mg/mL (2-mL amp), LOU 4

Tablet (scored), 5 mg, LOU 4

Indications and dose

Adult

Status epilepticus, emergency management of recurrent epileptic seizures, by slow IV injection (at a rate of 5 mg/min): 10–20 mg, repeated, if necessary, after 30–60 minutes, may be followed by IV infusion up to a maximum of 3 mg/kg over 24 hours

Status epilepticus, emergency management of recurrent epileptic seizures by rectum as solution: 500 micrograms/kg, if convulsions not controlled, other measures should be instituted.

- **Elderly:** 250 micrograms/kg, repeated, if necessary, every 12 hours, if convulsions not controlled, other measures should be instituted

Drug or alcohol withdrawal, by slow IV injection (at a rate of 5 mg/min): 10 mg, higher doses may be required, depending on severity of symptoms

Seizures associated with poisoning, by slow IV injection (at a rate of 5 mg/min): 10–20 mg

Muscle spasm of varied etiology, oral: 5–15 mg daily in divided doses, then increased if necessary to 60 mg daily, adjusted according to response, dose only increased in spastic conditions

Acute muscle spasm, by IM injection, or by slow IV injection: 10 mg, then 10 mg after 4 hours if required, IV injection to be administered into a large vein at a rate of no more than 5 mg/min

Tetanus, by IV injection: 100–300 micrograms/kg every 1–4 hours

Anxiety, oral: 5 mg a day, then increased if necessary to 15–30 mg daily in divided doses

Insomnia associated with anxiety, oral: 5–15 mg daily, to be taken at bedtime

Paediatric

Status epilepticus, emergency management of recurrent seizures, rectal

Neonate 1.25–2.5 mg repeated once after 10 minutes if necessary

Infant or **child <2 years:** 5 mg repeated once after 10 minutes if necessary **Older than 2 years**: 10 mg repeated once after 10 minutes if necessary

Note: Repeat doses should only be administered under medical supervision.

Tetanus, by IV injection

100–300 micrograms/kg every 1–4 hours

Muscle spasm in cerebral spasticity or in postoperative skeletal muscle spasm, oral

Child 1–11 months: Initially 250 micrograms/kg twice daily

Child 1–4 years: Initially 2.5 mg twice daily

Child 5–11 years: Initially 5 mg twice daily

Child 12–17 years: Initially 10 mg twice daily, maximum 40 mg per day.

Contraindications: CNS depression or coma, shock, respiratory depression, acute pulmonary insufficiency, sleep apnoea, severe hepatic impairment, marked neuromuscular respiratory weakness including unstable myasthenia gravis

Precautions

- Respiratory disease, muscle weakness and myasthenia gravis, marked personality disorder, hepatic impairment, renal impairment; close observation required until full recovery after sedation, porphyria, neonates, and infants
- Skilled tasks: Warn patient or caregiver about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike or operating machinery, for 24 hours.

Hepatic impairment

- Reduce dose as may precipitate coma.
- Severe impairment: Avoid use.

Renal impairment: Severe impairment, consider dose reduction; increased cerebral sensitivity

Adverse effects: Drowsiness, sedation, confusion, amnesia, muscle weakness, ataxia, slurred speech, respiratory depression especially with repeat doses, hypotension, paradoxical insomnia, excitability, hallucinations, aggression, injection pain, thrombophlebitis, blood dyscrasias including neutropenia, agranulocytosis, anaemia, leukopenia and thrombocytopenia

Interactions with other medicines (*indicates serious): Amitriptyline, chlorpheniramine, chlorpromazine, codeine, enalapril, furosemide, haloperidol, halothane, isoniazid, ketamine, morphine, nitrous oxide, phenytoin, rifampicin, *ritonavir, spironolactone, thiopental

Note: Diazepam is a representative benzodiazepine anticonvulsant. Various drugs can serve as alternatives.

Gabapentin

ATC code: N03AX12

Tablet, 300 mg, LOU 4

Indications and dose

Adult

Adjunctive treatment of focal seizures with or without secondary generalization, oral: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3; alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day)

Monotherapy for focal seizures with or without secondary generalization, oral: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response, usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day)

Peripheral neuropathic pain, oral: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response, maximum 3.6 g per day continued

Menopausal symptoms, particularly hot flushes, in women with breast cancer, oral: 300 mg 3 times a day, initial dose should be lower and titrated up over 3 days

Oscillopsia in multiple sclerosis, oral: Initially 300 mg once daily, then increased in steps of 300 mg, every 4–7 days, adjusted according to response, usual maximum 900 mg 3 times a day

Spasticity in multiple sclerosis, oral: Initially 300 mg once daily for 1–2 weeks, then 300 mg twice daily for 1–2 weeks, then 300 mg 3 times a day for 1–2 weeks, alternatively initially 100 mg 3 times a day, then increased in steps of 100 mg 3 times a day, every 1–2 weeks, adjusted according to response, usual maximum 900 mg 3 times a day

Paediatric

Adjunctive treatment of focal seizures with or without secondary generalization, oral

Child 6–11 years: 10 mg/kg once daily (max. per dose 300 mg) on day 1, then 10 mg/kg twice daily (max. per dose 300 mg) on day 2, then 10 mg/kg 3 times a day (max. per dose 300 mg) on day 3, usual dose 25–35 mg/kg daily in 3 divided doses, some children may not tolerate daily increments, longer intervals (up to weekly) may be more appropriate, daily dose maximum to be given in 3 divided doses, maximum 70 mg/kg per day

Child 12–17 years: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day); some children may not tolerate daily increments, longer intervals (up to weekly) may be more appropriate

Monotherapy for focal seizures with or without secondary generalization, oral

Child 12–17 years: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response, usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day), some children may not tolerate daily increments, longer intervals (up to weekly) may be more appropriate.

Precautions Diabetes mellitus, elderly, high doses of oral solution in adolescents and adults with low body weight, history of psychotic illness, history of substance abuse, mixed seizures (including absences)

Renal impairment

- Dose adjustments in adults, reduce dose to 600–1800 mg daily in 3 divided doses if creatinine clearance (CrCl) 50–79 mL/min.
- Manufacturer advises reduce dose to 300–900 mg daily in 3 divided doses if CrCl 30–49 mL/min.
- Manufacturer advises reduce dose to 150–600 mg daily in 3 divided doses if CrCl 15–29 mL/min (150 mg daily dose to be given as 300 mg in 3 divided doses on alternate days).
- Reduce dose to 150–300 mg daily in 3 divided doses if CrCl <15 mL/min (150 mg daily dose to be given as 300 mg in 3 divided doses on alternate days); further dose reductions may be required in proportion to CrCl, consult product literature.
- In **children,** reduce dose if EGFR <80 mL/min/1.73 m2, consult product literature.

Pregnancy: Avoid unless benefit outweighs risk; toxicity reported

Breastfeeding: Present in milk—manufacturer advises use only if potential benefit outweighs risk.

Adverse reactions: Anxiety, appetite abnormal, arthralgia, asthenia, behavior abnormal, confusion, constipation, cough, depression, diarrhea, dizziness, drowsiness, dry mouth, dysarthria, dyspnea, emotional lability, flatulence, gait abnormal, GI discomfort, headache, hypertension, increased risk of infection, insomnia, leucopenia, malaise, movement disorders, muscle complaints, nausea, nystagmus, edema, pain, reflexes abnormal, seizure (in children), sensation abnormal, sexual dysfunction, skin reactions, thinking abnormal, tooth disorder tremor, vasodilation, vertigo, visual impairment, vomiting, cognitive impairment, palpitations

Interactions with other medicines and additional notes: See Gabapentin Section 6: Anticonvulsants/Antiepileptics

Haloperidol

ATC code: N05AD01

Injection, 5 mg in 1-mL amp, LOU 3

Tablet (scored), 5 mg, LOU 3

Indications and dose

Schizophrenia and other psychotic disorders, short-term adjunctive management of psychomotor agitation, excitement, violent, dangerous or impulsive behaviour and severe anxiety, motor tics (including Tourette syndrome)

Adult

Schizophrenia and other psychoses, mania, short-term adjunctive management of psychomotor agitation, violent behaviour, and severe anxiety, oral: 2.5–5 mg 2–3 times daily

For elderly or debilitated patients, use half of the adult dose; 3–5 mg 2–3 times daily in severely affected or resistant patients, up to 30 mg daily in resistant schizophrenia

Acute psychotic conditions by IM injection: Initially 2–10 mg (half of the adult dose in elderly or debilitated patients, up to 18 mg in severely affected patients), subsequent doses every 4–8 hours according to response (up to every hour if necessary) up to a maximum of 18 mg daily

Paediatric

Schizophrenia and other psychoses, short-term adjunctive management of psychomotor agitation, excitement and violent or dangerous impulsive behaviour, severe anxiety, oral

Child 3–12 years: Initially 0.125–0.25 mg twice daily, increase by 0.25–0.5 mg/day every 5–7 days; maximum 0.15 mg/kg daily; usual maintenance 0.025–0.05 mg/kg three times daily

IM (when rapid effect required)

Child 6–12 years: 1–3 mg per dose every 4–8 hours to a maximum of 0.15 mg/kg daily; change to oral therapy as soon as possible

Motor tics (including Tourette syndrome), oral

Child 5–12 years: 0.0125–0.025 mg/kg twice daily, adjusted according to response up to 10 mg daily
Contraindications: Impaired consciousness due to CNS depression, bone marrow depression, phaeochromocytoma, porphyria, basal ganglia disease, severe liver or cardiac disease

Precautions

- Cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, renal and hepatic impairment (avoid if severe), history of jaundice, leukopenia (blood count required if unexplained fever or infection), hypothyroidism, myasthenia gravis, prostatic hypertrophy, closed-angle glaucoma, subarachnoid haemorrhage, metabolic disturbances such as hypokalaemia, hypocalcaemia or hypomagnesaemia, avoid abrupt withdrawal, patients should remain supine and have their blood pressure monitored for 30 minutes after IM injection.
- Skilled tasks: Warn patient or caregiver about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike or operating machinery.

Hepatic impairment: Can precipitate coma, consider dose reduction; avoid use in severe impairment

Renal impairment: Severe: start with small doses, increased cerebral sensitivity

Adverse effects

- Common: Sedation, anxiety, agitation, extrapyramidal adverse effects (see below), orthostatic hypotension, tachycardia, blurred vision, mydriasis, constipation, nausea, dry mouth, urinary retention, weight gain, hyperprolactinaemia (may result in galactorrhoea, gynaecomastia, amenorrhoea or infertility)
- Rare: Allergic reactions, including urticaria, SJS, corneal and lens opacities, SIADH, hyperthermia, hypothermia, neuroleptic malignant syndrome, anaemia, thrombocytopenia, agranulocytosis, venous thromboembolism, ECG changes (reversible, broadened QT interval), arrhythmias, cardiac arrest, sudden death, hepatic fibrosis, priapism, SLE, seizures, increased blood glucose (see metabolic effects below), dysarthria, dysphagia, weight loss, hypoglycaemia
- Extrapyramidal adverse effects: Reduce antipsychotic dose to avoid recurrent extrapyramidal adverse effects when possible.

Interactions with other medicines (*indicates serious): *Amitriptyline, *artemether + lumefantrine, atropine, *carbamazepine, *clomipramine, codeine, diazepam, dopamine, enalapril, epinephrine, *erythromycin, ethanol, *ethosuximide, *fluoxetine, *halothane, *ketamine, *metoclopramide, morphine, nifedipine, *nitrous oxide, *phenobarbital, *phenytoin, *procainamide, *quinidine, *rifampicin, *ritonavir, *thiopental, *valproic acid

Hyoscine Butylbromide

ATC code: A03BB01

Tablet, 10 mg, LOU 3

Injection, 20 mg/1 mL, LOU 3

Indications and dosage

Adult

Smooth muscle spasm, oral: 20 mg four times daily

Irritable bowel syndrome: 10 mg 3 times daily, increase if required up to 20 mg 4 times daily

IM or IV, acute spasm and spasm in diagnostic procedures: 20 mg repeated after 30 minutes if necessary; may be repeated more frequently in endoscopy; maximum 100 mg daily

Paediatric

Acute spasm, spasm in diagnostic procedures, initially by IM injection or by slow IV injection **Child 2–5 years:** 5 mg, then (by IM injection or by slow IV injection) 5 mg after 30 minutes if required, dose may be repeated more frequently in endoscopy, maximum 15 mg per day

Child 6–11 years: 5–10 mg, then (by IM injection or by IV injection) 5–10 mg after 30 minutes if required, dose may be repeated more frequently in endoscopy, maximum 30 mg per day

Bowel colic in palliative care, oral

Child 1 month–1 year: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg) **Child 2–4 years:** 5 mg 3–4 times a day

Child 5–11 years: 10 mg 3–4 times a day

Child 12–17 years: 10–20 mg 3–4 times a day

Bowel colic in palliative care, by IM injection or IV injection

Child 1 month–4 years: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg) **Child 5–11 years:** 5–10 mg 3–4 times a day

Child 12–17 years: 10–20 mg 3–4 times a day

Contraindications/precautions: Pregnancy, geriatric patient, hyperthyroidism, dysrhythmias, ulcerative colitis, hypertension, renal disease, hepatic disease, urinary retention

Adverse effects: Headache, confusion, dizziness, hallucination, palpitation, tachycardia, blurred vision, tachycardia, blurred vision, photophobia, cycloplegia, dry mouth, constipation, paralytic ileus

Interactions with other medicines: CNS depressants.

Lactulose

ATC code: A06AD11

Oral liquid, 3.1–3.7 g/5 mL, LOU 4

Indications and dose

Adult

Constipation oral: Initially 15 mL twice daily, adjusted according to response.

Hepatic encephalopathy (portal systemic encephalopathy), oral: Adjusted according to response to 30–50 mL 3 times a day, subsequently adjusted to produce 2–3 soft stools per day

Paediatric

Constipation, oral

Child 1–11 months: 2.5 mL twice daily, adjusted according to response

Child 1–4 years: 2.5–10 mL twice daily, adjusted according to response

Child 5–17 years: 5–20 mL twice daily, adjusted according to response

Hepatic encephalopathy (portal systemic encephalopathy), oral

Child 12–17 years: Adjusted according to response to 30–50 mL 3 times a day, subsequently adjusted to produce 2–3 soft stools per day

Contraindications: Galactosaemia, GI, obstruction, GI perforation, risk of GI perforation

Precautions: Lactose intolerance

Drug interactions: Do not use with other laxatives (hepatic encephalopathy), increased chance of GI obstruction with nifedipine.

Adverse effects: Common or very common, abdominal pain, diarrhea, flatulence, nausea, vomiting, electrolyte imbalance

Note: Use in pregnancy, not known to be harmful; may take up to 48 hours to act

Loperamide

ATC code: A07DA03

Capsule, 2 mg, LOU 3

Indications and dose

Adult

Acute nonspecific diarrhoea, chronic diarrhoea, faecal incontinence, pain of intestinal colic

Acute diarrhoea, oral: Initially 4 mg, followed by 2 mg for up to 5 days, usual dose 6 to 8 mg daily, maximum 16 mg per day

Chronic diarrhoea, oral: Initially 4 to 8 mg daily in divided doses, subsequently adjusted accordance to response, maintenance up to 16 mg daily in 2 divided doses

Paediatric

CAUTION: Not recommended for children under 12 years

Chronic diarrhoea, oral

Child over 2 years: Initially 1 mg/12.5 kg body mass, followed by 0.5 mg/12.5 kg after each loose stool; alternatively, 0.08–0.24 mg/kg/day in 2–3 divided doses

Symptomatic treatment of acute diarrhea, oral

Child 4–7 years: 1 mg 3–4 times a day for up to 3 days only

Child 8–11 years: 2 mg 4 times a day for up to 5 days

Contraindications/precautions

» Active ulcerative colitis, antibiotic associated colitis, condition where abdominal distention develops, condition where inhibition of peristalsis should be avoided, hypersensitivity, bloody diarrhoea, high fever, infectious diarrhoea, pseudomembranous colitis, age <2 years

» Patients in whom constipation must be avoided.

» Avoid use as primary therapy with acute dysentery.

» Discontinue if no improvement seen within 48 hours in patient with acute diarrhoea, symptoms worsen, or abdominal swelling or bulging develops.

Adverse effects: Dizziness, drowsiness, fatigue, flatulence, headache, nausea

Interactions: Eluxadoline and fentanyl increase chance and severity of constipation; opioid analgesics, CNS depressants (e.g., alcohol)

Note: If no improvement has been observed after treatment with 16 mg daily for at least 10 days, further administration is unlikely to be beneficial.

Metoclopramide

ATC code: A03FA01

Injection, 5 mg/mL (2-mL amp), LOU 4

Tablet, 10 mg, LOU 2

Indications and dose

Adult

Nausea and vomiting in GI disorders, in migraine and following surgery and treatment with cytotoxics or radiotherapy, gastro-oesophageal reflux disease (GERD) premedication, aid to GI intubation, gastroparesis, by oral, by IM injection, or by slow IV injection (over 1–2 minutes)

Young adult 15–19 years (under 60 kg): 5 mg 3 times daily

Adult: 10 mg 3 times daily

Premedication, by slow IV injection: 10 mg as a single dose

Aid to GI intubation, oral, by IM injection, or by slow IV injection

Young adult 15–19 years: 10 mg as a single dose 5–10 minutes before examination

Adult: 10–20 mg as a single dose 5–10 minutes before examination

Paediatric

See section 19.2: Metoclopramide

Contraindications: GI obstruction, haemorrhage or perforation, 3–4 days after GI surgery, convulsive disorders, phaeochromocytoma

Precautions: Elderly, children, and young adults; hepatic impairment, renal impairment, may mask underlying disorders, such as cerebral irritation; avoid for 3–4 days after GI surgery; pregnancy and breastfeeding, Parkinson disease, epilepsy, depression, porphyria

Adverse effects: Extrapyramidal symptoms (especially in children and young adults, see introductory note above), tardive dyskinesias on prolonged use, hyperprolactinaemia, drowsiness, restlessness,

dizziness, headache, diarrhoea, depression, hypotension and hypertension reported, rarely neuroleptic malignant syndrome, rash, pruritus, oedema, cardiac conduction abnormalities following IV administration, rarely methaemoglobinaemia (more severe in G6PD deficiency).

Interactions: Increases anticholinergic response of atropine and other anticholinergics; metoclopramide, phenothiazines decreases effect of amantadine

Note: Metoclopramide should only be prescribed for short-term use (up to 3 days). Thereafter, review need for use. Not for use in children.

Midazolam

ATC code: N05CD08

Injection, 1 mg (as HCl)/1 mL (5-mL amp), LOU 5

Indications and dose:

Adult

Delirium and terminal restlessness in palliative care, SC infusion **(off-license use: Consult a specialist)**: Initially 10-20 mg in 24 hours, adjusted according to response; usual dose 20-60mg in 24 hours

Paediatric

Off-license use: Consult a specialist

Contraindications, Precautions, Pregnancy, Breastfeeding, Adverse effects, Interactions with other medicines and Notes: *See section 1: Anaesthetics, pre- & intra-operative medicines, and medical gases*

Ondansetron

ATC code: A04AA01

Injection, 2 mg (as HCl)/mL (2-mL amp), LOU 2

Ondansetron oral liquid, 4 mg base/5 mL, LOU 2

Ondansetron tablet, 4 mg (as HCl), LOU 2

Indications and dose

For the prevention of nausea and vomiting associated with moderately-to highly emetogenic cancer chemotherapy, radiotherapy in patients receiving total body irradiation or fractions to the abdomen and post-operation; also used for the treatment of post-operative nausea and vomiting

Adult

Moderately emetogenic chemotherapy or radiotherapy, oral: 8 mg 1–2 hours before treatment or by IM injection or slow IV injection, 8 mg immediately before treatment then oral, 8 mg every 12 hours for up to 5 days.

Severely emetogenic chemotherapy, by IM injection or slow IV injection: 8 mg immediately before treatment, where necessary, followed by 2 further doses of 8 mg at intervals of 2–4 hours (or followed by 1 mg/hour by continuous IV infusion for up to 24 hours), then oral, 8 mg every 12 hours for up to 5 days; alternatively, by IV infusion, over at least 15 minutes, 32 mg immediately before treatment then oral, 8 mg every 12 hours for up to 5 days

Prevention of postoperative nausea and vomiting, oral: 16 mg 1 hour before anaesthesia or 8 mg 1 hour before anaesthesia, followed by 8 mg at intervals of 8 hours for 2 further doses; alternatively, by IM or slow IV injection, 4 mg at induction of anaesthesia

Paediatric

Note: Use only in children aged >6 months

Chemotherapy-induced nausea and vomiting

Child 6 months–18 years: *By IV infusion* over 15 minutes, 5 mg/m2 (max. 8 mg) immediately before chemotherapy, then for body-surface area <0.6 m2, 2 mg oral every 12 hours for up to 5 days; for body-surface area 0.6 m2 or greater, 4 mg oral every 12 hours for up to 5 days, max. total daily dose 32 mg; alternatively, by IV infusion over 15 minutes, 150 micrograms/kg (max. 8 mg) immediately before chemotherapy repeated at intervals of 4 hours for 2 further doses, then for body weight 10 kg or less 2 mg oral every 12 hours for up to 5 days; for body weight over 10 kg, 4 mg oral every 12 hours for up to 5 days, maximum total daily dose 32 mg

Prevention of postoperative nausea and vomiting

Child 6 month–18 years: By slow IV injection over at least 30 seconds, 100 micrograms/kg (max. 4 mg) before, during, or after induction of anaesthesia

Treatment of postoperative nausea and vomiting by IM or slow IV injection

Child 6 month–18 years: By slow IV injection over at least 30 seconds, 100 micrograms/kg (max. 4 mg)

Contraindications: Hypersensitivity to medicine, other selective 5-HT3 antagonists, or any component of the formulation

Precautions: Avoid concomitant use of medicines that prolong QT interval, sub-acute intestinal obstruction, adenotonsillar surgery, in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents, in patients with significant electrolyte disturbance, in patients with hepatic impairment, pregnancy, breastfeeding

Hepatic impairment: Moderate and severe impairment: Reduce dose

Renal impairment: No dose reduction required.

Adverse effects

- Common: Constipation, headache, transient rise in hepatic aminotransferases.
- Uncommon: Hiccups, hypotension, chest pain, diarrhoea.
- Rare: Hypersensitivity reactions (including anaphylaxis), arrhythmias, ECG changes, extrapyramidal effects, seizures, transient visual disturbances, e.g., blurred vision (with rapid IV administration)

Interactions with other medicines: Apomorphine, CYP3A4-inducers (such as aminoglutethimide, carbamazepine, nafcillin, nevirapine, phenobarbital, phenytoin, and rifampicin), tramadol

Notes

- Administration for slow IV injection, give over 2–5 minutes; for IV infusion, dilute to a

concentration of 320–640 micrograms/mL with glucose 5% or sodium chloride 0.9%, give over at least 15 minutes.

» Not for use in first trimester of pregnancy.

Prednisolone

ATC code: H02AB06

Oral liquid, 15 mg/5 mL, LOU 4

Tablet, 5 mg, LOU 4

Indications and dose

Suppression of inflammatory and allergic disorders, inflammatory bowel disease, asthma, and rheumatic disease, for the treatment of adrenocortical insufficiency and as immune suppression.

Adult

Oral administration: Initially up to 10–20 mg daily (severe disease, up to 60 mg daily), preferably taken in the morning after breakfast; dose can often be reduced within a few days, but may need to be continued for several weeks or months; maintenance, 2.5–15 mg daily or higher, cushingoid features are increasingly likely with doses above 7.5 mg daily

Paediatric

Oral

Infant or **child:** 1–2 mg/kg once daily (usual maximum 60 mg), reducing after a few days if appropriate; increased frequency may be required in certain clinical indications

Contraindications: Untreated systemic infection; administration of live vaccines: usually not relevant to emergency treatment

Precautions

» Most precautions do not apply for emergency or short-term use.

» Increased severity of viral infections, recent MI, congestive heart failure, renal impairment, hepatic impairment, diabetes mellitus, osteoporosis, glaucoma, corneal perforation, severe psychosis, epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Adverse effects more common.

Adverse effects

» Incidence of adverse effects is related to dose and duration of treatment.

» Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.

» Common: Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects (including euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behavior)

» Rare: Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions including anaphylaxis, psychiatric effects (including delirium and psychosis).

Interactions with other medicines (* indicates serious):

Acetylsalicylic acid: Increased risk of gastrointestinal bleeding and ulceration, prednisolone reduces plasma salicylate concentration

*Amphotericin B: Increased risk of hypokalaemia

*Carbamazepine: Accelerated metabolism of prednisolone (reduced effect)

Ciclosporin: Increased plasma concentration of prednisolone

Contraceptives, oral: Those containing estrogens increase plasma concentration of prednisolone.

Digoxin: Increased risk of hypokalaemia

Enalapril: Antagonism of hypotensive effect

Erythromycin: Possibly inhibits metabolism of prednisolone

Furosemide: Antagonism of diuretic effect, increased risk of hypokalaemia

Hydrochlorothiazide: Antagonism of diuretic effect, increased risk of hypokalaemia

Ibuprofen: Increased risk of gastrointestinal bleeding and ulceration

Insulins: Antagonism of hypoglycaemic effect

*Methotrexate: Increased risk of haematological toxicity

*Phenobarbital: Metabolism of prednisolone accelerated (reduced effect)

*Phenytoin: Metabolism of prednisolone accelerated (reduced effect)

Propranolol: Antagonism of hypotensive effect

*Rifampicin: Accelerated metabolism of prednisolone (reduced effect)

Ritonavir: Plasma concentration possibly increased by ritonavir

Salbutamol: Increased risk of hypokalaemia if high doses of salbutamol given with prednisolone

Spironolactone: Antagonism of diuretic effect

Infuenza vaccine: High doses of prednisolone impair immune response

*Live vaccines: High doses of prednisolone impair immune response, avoid use of live vaccines

*Warfarin: Anticoagulant effect possibly enhanced or reduced (high-dose prednisolone enhances anticoagulant effect)

Notes

» Take the tablets or oral liquid with food to reduce stomach upset.

Pregabalin

ATC Code: N02BF02

Capsule, 25mg, 75mg, LOU 5

Indications and dose

Adult

Diabetic peripheral neuropathic pain, oral: Initially 50 mg every 8 hours. Maintenance: May increase to 100 mg every 8 hours within 1 week, as needed; do not to exceed 300 mg in 24hours.

Post herpetic neuralgia, oral: Initially 150-300 mg daily in 2-3 divided doses (every 8 – 12 hours); do not exceed 300mg in 24 hours.

Neuropathic pain with spinal cord injury, oral: Initially 75 mg every 12 hours (150mg in 24 hours). May increase within 1 week to 300 mg daily in 2 divided doses. If there is insufficient pain relief after 2-3 weeks and 300 mg/day dose is tolerated, may increase dose again up to 600 mg/day in 2 divided doses.

Paediatric

Safety and efficacy not established.

Contraindications: Hypersensitivity to the active substance or to any of the excipients

Precautions: Asthenia, Edema, Facial edema, Hypotension, Neuropathy, Pain, Disorientation, Constipation, Weight gain, Confusion, Amnesia, Vertigo, Addiction, Anemia, Diarrhea, Gynecomastia and breast enlargement, Epididymitis, Esophagitis, Dysmenorrhea, Dystonia, Heart failure.

Pregnancy: There are no adequate and well-controlled studies with pregabalin in pregnant women

Breastfeeding: Small amounts of pregabalin have been detected in the milk of lactating women

Adverse effects: Common or very common: abdominal distension, appetite abnormal, asthenia, cervical spasm, concentration impaired, confusion, constipation, diarrhoea, dizziness, drowsiness, dry mouth, feeling abnormal, gait abnormal, gastrointestinal disorders, headache, increased risk of infection, joint disorders, memory loss, mood altered, movement disorders, muscle complaints, nausea, oedema, pain, sensation abnormal, sexual dysfunction, sleep disorders, speech impairment, vertigo, vision disorders, vomiting, weight changes. Uncommon: aggression, anxiety, arrhythmias, atrioventricular block, breast abnormalities, chest tightness, chills, consciousness impaired, cough, depression, dry eye, dyspnoea, epistaxis, eye discomfort, eye disorders, eye inflammation, fever, hallucination, hyperacusia, hyper-/hypo-tension, hypoglycaemia, malaise, menstrual cycle irregularities, nasal complaints, neutropenia, oral disorders, peripheral coldness, psychiatric disorders, reflexes decreased, skin reactions, snoring, sweat changes, syncope, taste loss, thirst, urinary disorders, vasodilation. Rare or very rare: altered smell sensation, ascites, dysgraphia, dysphagia, gynaecomastia, hepatic disorders, pancreatitis, pulmonary oedema, QT interval prolongation, renal impairment, rhabdomyolysis, Stevens-Johnson syndrome, throat tightness. Frequency not known: drug use disorders, encephalopathy, respiratory depression, suicidal behaviours, withdrawal syndrome

Interactions with other medicines (*indicates serious): *enalapril, *captopril, *lisinopril, *metoclopramide, alprazolam, amitriptyline.

Senna

ATC Code: A06AB06

Tablet, 7.5 mg, LOU, 4

Indications and dose

Adult

Constipation (opioid induced), oral: 7.5-15 mg once daily, at bedtime; maximum per dose 30 mg daily. Higher doses may be prescribed under medical supervision.

Paediatric

Constipation, oral:

Tablets not licensed for use in children under 6 years.

Child 6-17 years: 7.5-30mg once daily, at bedtime, adjusted according to response. Not for use of greater than 1 week.

Contraindications: Hypersensitivity to the active substance or to any of the excipients, not to be used at the same time as other laxative agents, GI obstruction or perforation, ulcerative colitis, symptoms of appendicitis or acute surgical abdomen, acute intestinal inflammation (Chron's disease), faecal impaction, GI or rectal bleeding.

Pregnancy: Use with caution if benefits outweigh risk

Breastfeeding: It is not excreted in breast milk.

Adverse effects: Abdominal pain, diarrhoea, electrolyte abnormalities, including hypokalaemia, excessive bowel activity, finger clubbing (long-term use), melanosis coli, nausea, nephritis, yellow-brown urine discoloration, hepatic impairment.

Interactions with other medicines (*indicates serious): *magnesium sulphate, *potassium chloride, *sodium sulphate, *polyethylene glycol, deflazacort, dichlorphenamide, digoxin, diuretics, adrenocorticosteroids and liquorice root.

4. Antiallergics & Medicines Used In Anaphylaxis

Cetirizine

ATC code: R06AE07

Tablet, 10mg, LOU 2

Oral liquid, 1mg/ml LOU 2

Indications and dose:

Adult: 10mg once daily

Symptomatic relief of perennial and seasonal allergies such as chronic idiopathic urticaria, atopic dermatitis, hay fever, vasomotor rhinitis, angioedema, allergic conjunctivitis, anaphylactic reactions, and relief of symptoms from colds, oral:

Paediatric:

Child 1 year: 250micrograms/kg twice daily.

Child 2 - 5years: 2.5mg twice daily

Child 6 - 11years: 5mg twice daily

Child 12 - 17years: 10mg once daily

Symptomatic relief of perennial and seasonal allergies such as chronic idiopathic urticaria, atopic dermatitis, hay fever, vasomotor rhinitis, angioedema, allergic conjunctivitis, anaphylactic reactions, and relief of symptoms from colds, oral:

Contraindications: Hypersensitivity to cetirizine hydrochloride.

Precautions: Avoid activities requiring mental alertness until accustomed to the drug since it may cause CNS depression. Alcohol, sedatives, and tranquilizers may cause an increased risk of drowsiness.

Hepatic impairment: Dose adjustment is not necessary in patients with solely hepatic impairment.

Renal impairment:

- GFR ≥ 50ml/min: Dose adjustment not necessary
- GFR ≤ 50ml/min: 5mg once daily
- Peritoneal dialysis: 5mg once daily
- Intermittent hemodialysis: 5mg once daily but may administer 5mg three times weekly.

Pregnancy: No adequate and well controlled studies in pregnant women, however the data available does not suggest potential for foetal and embryonic toxicity.

Breastfeeding: It is excreted in human breastmilk and the concentrations can range from 25% to 90% of those measured in plasma. Use with caution.

Adverse effects: Somnolence, headache, agitation, aggression, fatigue, malaise, diarrhea, paresthesia, skin reactions, dry mouth, bronchospasms and epistaxis. Other rare adverse effects include: stomach pain, angioedema, tongue discoloration and tremors.

Interactions with other medicines (*indicates serious): Olopatadine intranasal*, metoclopramide intranasal*, isocarboxazid*. Consider using alternatives.

Notes: Caution should be exercised in epileptic patients and patients who are at risk of convulsions.

Chlorpheniramine

ATC code: R06AB04

Injection, 10 mg (maleate) in 1-mL amp, LOU 2

Oral liquid, 2 mg (as maleate)/5 mL, LOU 2

Indications and dose

Adult

Allergic reactions, anaphylaxis (adjunct), by SC, IM, or IV injection: 10 to 20 mg (maximum 40 mg in 24 hours)

Paediatric

Allergy, oral:

Child under 1 year: Not recommended

Child 1 to 2 years: 1 mg twice daily

Child 2 to 6 years: 1 mg every 4 to 6 hours (maximum 6 mg daily)

Child 6 to 12 years: 2 mg every 4 to 6 hours (maximum 12 mg daily)

Allergic reactions, anaphylaxis (adjunct), by SC, IM, or IV injection

Child under 1 year: Not recommended

Child 1 to 6 years: 2.5 to 5 mg

Child 6 to 12 years: 5 to 10 mg

Contraindications: Hypersensitivity to chlorpheniramine or dexchlorpheniramine

Precautions: Asthma, bladder neck obstruction, hepatic insufficiency, narrow angle glaucoma, pyloroduodenal obstruction, sedative effects, stenosing peptic ulcer, symptomatic prostatic hypertrophy

Hepatic impairment: Sedation caused by chlorpheniramine inappropriate in severe liver disease, avoid.

Renal impairment: Severe: dose reduction may be required

Pregnancy: Use in the latter part of third trimester may cause adverse effects in neonates, such as irritability, paradoxical excitability, and tremor.

Breastfeeding: May be present in breast milk, not known to be harmful

Adverse effects: Anorexia, nausea, vomiting, epigastric distress, diarrhoea, constipation, drowsiness, somnolence, dry mouth, blurred vision, urinary retention, drying effect throughout the respiratory tract and a thickening of bronchial mucus, headache, weight gain, exfoliative dermatitis, cardiac dysrhythmia, hypotension (more severe when used intravenously), paradoxical excitation, disturbances in smell and taste, facial dyskinesias, blood dyscrasias (including agranulocytosis, thrombocytopenia, pancytopenia and aplastic anaemia), EEG changes, psychotic disorder, liver dysfunction, tremor, seizures,

confusion, depression, sleep disturbances

Interactions with other medicines (*indicates serious): Amitriptyline, atropine, diazepam, lopinavir

Notes

- Warn patient or caregiver about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike or operating machinery, for 24 hours.
- Also referred to as chlorpheniramine maleate
- Give IV injection over 1 minute
- If necessary, injection solution can be diluted with sodium chloride 0.9% injection.
- Chlorpheniramine may cause excitability in children.
- WHO age/weight restriction: > 1 year

Dexamethasone

ATC code: H02AB02

Injection, 4 mg (as sodium phosphate)/mL amp, LOU 4

Indications and dose

Adult

IM or slow IV injection or infusion: Adjunct in the emergency treatment of anaphylaxis, 0.5 to 24 mg

Paediatric

Inflammatory and allergic disorders

Infant or **child**: 0.1 to 0.4 mg/kg in 1 to 2 divided doses (maximum 24 mg daily)

IM, or slow IV injection or infusion, adjunct in the emergency treatment of anaphylaxis

Child: 0.2to 0.4 mg/kg.

Contraindications: Not relevant to emergency use.

Precautions: Increased susceptibility to and severity of infection, activation or exacerbation of TB, amoebiasis, strongyloidiasis, risk of severe chickenpox in non-immune patients (varicella zoster immunoglobulin required if exposed to chickenpox), avoid exposure to measles (normal immunoglobulin possibly required if exposed), diabetes mellitus, peptic ulcer, hypertension, corneal perforation, osteoporosis, myasthenia gravis

Hepatic impairment: Dose reduction not necessary

Renal impairment: Dose reduction not necessary

Pregnancy: Readily crosses the placenta

Adverse effects

- Incidence of adverse effects is related to dose and duration of treatment.
- Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.
- Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects, transient itching, burning or tingling in perineal area (after IV bolus), posterior subcapsular cataracts, glaucoma, hypersensitivity reactions including anaphylaxis; psychiatric effects include euphoria, hypomania, depression, disturbances of mood, cognition, sleep, and behaviour

Interactions with other medicines (*indicates serious): Acetylsalicylic acid, albendazole, *amphotericin B, *carbamazepine (accelerated metabolism of dexamethasone, reduced effect), oral contraceptives, digoxin, enalapril, erythromycin, furosemide, hydrochlorothiazide, ibuprofen, influenza vaccine, insulins, *live vaccines, *lopinavir, metformin, *methotrexate, *phenobarbital, *phenytoin, praziquantel, propranolol, *rifampicin, ritonavir, salbutamol, saquinavir, spironolactone, infuenza vaccine, live vaccines, warfarin

Diphenhydramine

ATC code: R06AA02

Injection, 50mg/mL, LOU 4

Indications and dose:

Indicated for the management of uncomplicated allergic reactions of the immediate type where oral therapy is contraindicated or impossible, allergic reactions to blood or plasma and as an adjunct to epinephrine and other standard measures in anaphylaxis

Adult:

By IV or deep IM

10-50mg every 4-6 hours at a rate not exceeding 25mg/min. Do not exceed 400mg per day.

Paediatric:

By IV or deep IM

5mg/kg /24hr. The maximum daily dose is 300mg. The total daily dose should be divided into 4 doses and administered intravenously at a rate not exceeding 25mg/min

Should not be used in neonates and premature infants.

Contraindications: Premature infants or neonates and breastfeeding mothers. Avoid in hypersensitivity.

Precautions: Can potentiate the effects of sedatives such as alcohol. CNS depression, avoid driving or operating heavy machinery. Used in caution in elderly patients due to anticholinergic effects that may exacerbate existing lower urinary tract conditions or benign prostrate hyperplasia. Increased risk of falls in the elderly.

Hepatic and renal impairment: No dose adjustments required.

Pregnancy: Not recommended in pregnancy, as crosses the placenta. Inadequate studies on use in pregnant women. Animal studies however show no risk to the foetus.

Breastfeeding: Present in breastmilk therefore contraindicated in breastfeeding mothers.

Adverse effects: Sedation, anticholinergic effects, confusion, decreased cognitive function in geriatric patients, pharyngeal dryness, dry nasal mucosa, palpitations, vertigo, tachycardia.

Interaction with other medicines:

- Potentiates the effects of other CNS depressants such as alcohol, anxiolytics, and hypnotics.
- Monoamine Oxidase Inhibitors may prolong and intensify the anticholinergic effects of diphenhydramine.
- Diphenhydramine has anti-muscarinic activity and may therefore potentiate the effects of some anticholinergic drugs such as atropine and Tri-cyclic antidepressants.
- Diphenhydramine inhibits Cytp450 isoenzyme Cyp2D6. There is therefore potential interaction for drugs metabolized by these enzymes.

Epinephrine (Adrenaline)

ATC code: C01CA24

Injection, 1mg/1mL amp, LOU 2

Indications and dose

Adult

Emergency treatment of acute anaphylaxis or angioedema (if laryngeal oedema is present)

IM injection: 500 micrograms (0.5 mg), to be injected preferably into the anterolateral aspect of the middle third of the thigh. Doses may be repeated several times, if necessary, at 5-minute intervals according to blood pressure, pulse, and respiratory function.

Acute anaphylaxis when there is doubt as to the adequacy of the circulation (specialist use only), angioedema (if laryngeal oedema is present) (specialist use only), slow IV injection

50 micrograms, using 0.5 mL of the dilute 1 in 10,000 epinephrine injection; dose to be repeated according to response; if multiple doses required, epinephrine should be given as a slow IV infusion, stopping when a response has been obtained.

Paediatric

Anaphylaxis, by IM injection

Infant under 6 months:50 micrograms (0.05 mL of 1 mg/mL solution)

Infant or **child 6 months to 6 years**: 150 micrograms (0.15 mL of 1 mg/mL solution)

Child 6 to 12 years: 300 micrograms (0.3 mL of 1 mg/mL solution); these doses may be repeated at 5-minute intervals, several times if necessary, depending on blood pressure, pulse and respiratory function.

Anaphylaxis, by slow IV injection

Infant or **child:** 10 micrograms/kg (0.1 mL/kg of the dilute 1 mg/10 mL solution) given over several minutes

Contraindications: Closed-angle glaucoma, use during halothane or cyclopropane anaesthesia

Precautions (for non-life-threatening situations): Hyperthyroidism, hypertension, diabetes mellitus, heart disease, arrhythmias, psychoneurosis, cerebrovascular disease, phaeochromocytoma, susceptibility to closed-angle glaucoma

Hepatic impairment: Dose reduction not necessary

Renal impairment: Dose reduction not necessary

Adverse effects

- Nausea, vomiting, anxiety, headache, fear, palpitations, tachycardia, restlessness, tremor, dizziness, dyspnoea, weakness, sweating, pallor, hyperglycaemia, excessive increase in blood pressure, ventricular arrhythmias, pulmonary oedema (on excessive dosage or extreme sensitivity), angina, cold extremities, peripheral ischaemia and necrosis (at injection site), allergic reaction (sodium metabisulfite in some products)
- Overdose or rapid IV administration: Arrhythmias (ventricular and supraventricular), severe hypertension, cerebral haemorrhage, pulmonary oedema

Interactions with other medicines (*indicates serious): Amitriptyline, *cyclopropane, *ergot derivatives, fluoxetine, *halothane, propranolol

Notes

- 1 mg/mL = 1:1000 or 0.1%.
- IV epinephrine should be used with extreme care by specialists only.
- IM epinephrine should be injected into anterolateral aspect of thigh; it should not be injected into hands, feet, ears, nose, genitals, or buttocks.

Hydrocortisone

ATC code: H02AB09

Powder for injection, 100-mg (as sodium succinate) vial, LOU 2

Indications and dose

Adult

Acute hypersensitivity reactions, such as angioedema of the upper respiratory tract and anaphylaxis (adjunct to epinephrine) IV injection: 100 to 300 mg, to be administered as sodium succinate

Paediatric

Adjunct in the emergency treatment of anaphylaxis, IM injection or IV injection

Infant under 6 months: Initially 25 mg up to 4 times daily adjusted according to response

Infant or **child 6 months to 6 years**: Initially 50 mg up to 4 times daily adjusted according to response

Child 6 to 12 years: Initially 100 mg up to 4 times daily adjusted according to response

Contraindications: Not relevant to emergency use

Precautions: Not relevant to emergency use

Hepatic impairment: Dose reduction not necessary

Renal impairment: Dose reduction not necessary

Adverse effects: See Dexamethasone

Interactions with other medicines (*indicates serious): *Influenza vaccine, see dexamethasone

Loratadine

ATC code: RO6AX13

Tablet, 10 mg, LOU 2

Indications and dose

Adult

Symptomatic relief of allergy such as hay fever, urticaria, oral: 10 mg daily

Paediatric

Symptomatic relief of allergy such as hay fever, urticaria, oral

Child 2 to 11 years (body weight up to 31 kg): 5 mg once daily

Child 2 to 11 years (body weight 31 kg and above): 10 mg once daily

Child 12 to 17 years: 10 mg once daily

Contraindications: Hypersensitivity to loratadine or any component of the formulation

Precautions: Rash, hives, itching, swelling of the eyes, face, lips, tongue, throat, hands, arms, feet, ankles, or lower legs; hoarseness, difficulty breathing or swallowing, wheezing

Hepatic impairment: Reduce initial dose to alternate days in severe hepatic impairment.

Renal impairment: Reduce dose if CrCl <50

Adverse effects: Drowsiness, nervousness (in children), increased headache (very common in children) and insomnia, alopecia, angioedema, dizziness, dry mouth, fatigue (very common in children), gastritis, hepatic function abnormalities, nausea, palpitations, rash, seizure, and tachycardia

Interactions with other medicines (*indicates serious): Acetylcholinesterase inhibitors, *aclidinium, alcohol (ethyl), amantadine, *amiodarone, amphetamines, *azelastine (nasal), betahistine, *bromperidol, *buprenorphine, *clozapine, doxylamine, *flunitrazepam, glucagon, *glycopyrrolate, *glycopyrronium (topical), hyaluronidase, hydroxyzine, *ipratropium, *itopride, ketoconazole (systemic), magnesium sulphate, metoclopramide, nitroglycerin, *opioid agonists, *oxycodone, *potassium chloride, *thalidomide, thiazide and thiazide-like diuretics, *tiotropium, *topiramate, *zolpidem

Prednisolone

ATC code: H02AB06

Oral liquid, 15 mg/5 mL, LOU 4

Tablet, 5 mg, LOU 4

Indications and dose

Adult

Allergy (short-term use), oral: Initially up to 10 to 20 mg daily as a single dose in the morning (in severe allergy, up to 60 mg daily as a short course of 5 to 10 days)

Paediatric

Allergy, oral

Infant or **child:** 1 to 2 mg/kg once daily (usual maximum 60 mg), reducing after a few days if appropriate; increased frequency may be required in certain clinical indications.

Contraindications: Untreated systemic infection, administration of live vaccines: usually not relevant to emergency treatment

Precautions

- Most precautions do not apply for emergency or short-term use.
- Increased severity of viral infections, recent MI, congestive heart failure, renal impairment, hepatic impairment, diabetes mellitus, osteoporosis, glaucoma, corneal perforation, severe psychosis, epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy.

Hepatic impairment: Adverse effects more common

Renal impairment: Dose reduction not necessary

Adverse effects

- Incidence of adverse effects is related to dose and duration of treatment.
- Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.
- Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects (including euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour), peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions including anaphylaxis, psychiatric effects (including delirium and psychosis)

Interactions with other medicines (*indicates serious): Acetylsalicylic acid, *amphotericin B, *carbamazepine, ciclosporin, digoxin, enalapril, erythromycin, furosemide, hydrochlorothiazide, ibuprofen, infuenza vaccine, insulins, live vaccines, methotrexate, oral contraceptives, phenobarbital, *phenytoin, propranolol, *rifampicin, ritonavir, salbutamol, spironolactone, *warfarin

Notes

- Tablets or oral liquid should be taken with food to reduce stomach upset.
- Prednisone should be considered equivalent to prednisolone.

5. Antidotes and Other Substances Used In Poisonings

The following notes on treatment of poisoning are guidelines only. It is strongly recommended that poison information centres or other local sources of expertise be consulted in cases of suspected poisoning.

A diagnosis of poisoning is based on history, including details of the poisoning agent, amount ingested, time of ingestion, and results of investigations when appropriate. Symptoms and signs depend on the agent involved and therefore vary widely.

Check for burns in or around the mouth, or stridor (abnormal respiratory sounds suggesting laryngeal damage), due to ingestion of corrosives. Admit all patients who have ingested iron, pesticides, paracetamol, aspirin, narcotics, antidepressant drugs, paraquat, lithium, or warfarin or who have taken modified-release or prolonged-release dose forms, even if they appear well. Patients who have ingested corrosives or petroleum products should not be sent home within 6 hours.

Supportive care

Few patients require active removal of the poison, and most are treated symptomatically with supportive care and monitoring of vital signs. Particular care must be given to maintenance of respiration and blood pressure. Assisted ventilation may be required. Cardiac conduction defects and arrhythmias often respond to correction of underlying hypoxia, acidosis, or other biochemical abnormalities. Hypothermia, which may develop in patients who have been unconscious for some hours, is best treated by wrapping the patient in blankets to conserve body heat. Convulsions, which are prolonged or recurrent, may be controlled by IV diazepam.

Initial stabilization

Airway and breathing

Respiration is often impaired in unconscious patients. An obstructed airway requires immediate attention. In the absence of trauma, the airway should be opened with simple measures, such as chin lift or jaw thrust. An oropharyngeal or nasopharyngeal airway may be useful in patients with reduced consciousness to prevent obstruction, provided ventilation is adequate. Intubation and ventilation should be considered in patients whose airway cannot be protected or who have respiratory acidosis because of inadequate ventilation; such patients should be monitored in a critical care area.

Most poisons that impair consciousness also depress respiration. Assisted ventilation (either mouth-to-mouth or using a bag-valve-mask device) may be needed. Oxygen is not a substitute for adequate ventilation, although it should be given in the highest concentration possible in poisoning with carbon monoxide and irritant gases.

IV naloxone (2 mg in adults, 0.1 mg/kg in children, doses as high as 10 mg may be necessary in some cases) should be tried in patients with apnea or severe respiratory depression while maintaining airway support. If respiratory depression persists despite use of naloxone, endotracheal intubation and continuous mechanical ventilation are required.

Circulation

Blood pressure: Hypotension is common in severe poisoning with CNS depressants. A systolic blood pressure of <70 mmHg may lead to irreversible brain damage or renal tubular necrosis. Hypotension should be corrected initially by raising the foot of the bed and administration of an infusion of either sodium chloride or a colloid. Fluid depletion without hypotension is common after prolonged coma and after aspirin poisoning due to vomiting, sweating, and hyperpnoea. Hypertension, often transient, occurs less frequently than hypotension in poisoning; it may be associated with sympathomimetic drugs, such as amfetamines, phencyclidine, and cocaine.

The first-choice vasopressor for most poison-induced hypotension is norepinephrine 0.5 to 1 mg/min IV infusion, but treatment should not be delayed if another vasopressor is more immediately available.

Heart: Cardiac conduction defects, and arrhythmias can occur in acute poisoning, notably with tricyclic antidepressants, some antipsychotics, and some antihistamines. Arrhythmias often respond to correction of underlying hypoxia, acidosis, or other biochemical abnormalities, but ventricular arrhythmias that cause serious hypotension require treatment. Dysrhythmias are frequently due to sodium channel blockade and may be treated with sodium bicarbonate. Alternately, they may be caused by potassium channel blockade - treat with magnesium sulphate (MgS04). If the QT interval is prolonged, specialist advice should be sought

Disability

Convulsions during poisoning: Single short-lived convulsions (lasting <5 minutes) do not require treatment. If convulsions are protracted or recur frequently, lorazepam or diazepam (preferably as emulsion) should be given by slow IV injection into a large vein. Benzodiazepines should not be given by the IM route for convulsions. If the IV route is not readily available, midazolam or mucosal solution can be given by the buccal route or diazepam can be administered as a rectal solution. Phenytoin is not recommended.

Methaemoglobinaemia: Drug- or chemical-induced methaemoglobinaemia should be treated with methylthioninium chloride if the methaemoglobin concentration is 30% or higher, or if symptoms of tissue hypoxia are present, despite oxygen therapy. In high doses, methylthioninium chloride can itself cause methaemoglobinaemia.

Thiamine (100 mg IV) should be given, with or before glucose, to adults with suspected thiamine deficiency (e.g., alcoholics, undernourished patients).

Decontamination

Depending on the substance involved and circumstances of poisoning, decontamination of the skin and eyes (with appropriate protection of staff and caregivers) should be undertaken. For inhaled poisons, removal from the source of poisoning, administration

of oxygen, and further airway support may be required.

Eye decontamination: Copious irrigation with saline. Instillation of local anaesthetic eye drops, and sedation may be required

Skin decontamination: Remove clothes, rinse with copious water, then soap and water

Gastric decontamination

Gastric decontamination (removal of poisons from the stomach) is most effective within 1 hour of ingestion; after this time, it is usually of little benefit. Administration of activated charcoal to prevent further absorption is the treatment of choice for gastric decontamination.

Induction of emesis for treatment of poisoning is not recommended.

Gastric lavage has a very limited role in treatment. It requires intubation for airway protection and should not be used without consultation.

Whole bowel irrigation has a limited role in treatment of life-threatening ingestions of some slow-release preparations and agents that do not bind to activated charcoal.

Alkaline diuresis enhances elimination of weak acids (e.g., salicylates, phenobarbital). A solution made by combining 1 L of 5% D/W with three 50-mEq (50 mmol/L) ampoules of sodium bicarbonate and 20 to 40 mEq (20 to 40 mmol/L) of potassium can be given at a rate of 250 mL/h in adults and 2 to 3 mL/kg/h in children. Urine pH is kept at >8, and potassium must be repleted. Hypernatremia, alkalemia, and fluid overload may occur but are usually not serious. However, alkaline diuresis is contraindicated in patients with renal insufficiency.

Dialysis: Common toxins that may require dialysis or hemoperfusion include ethylene glycol, lithium, methanol, salicylates, and theophylline. These therapies are less useful if the poison is a large or charged (polar) molecule, has a large volume of distribution (i.e., if it is stored in fatty tissue), or is extensively bound to tissue protein (as with digoxin, phencyclidine, phenothiazines, or tricyclic antidepressants). The need for dialysis is usually determined by both laboratory values and clinical status. Methods of dialysis include hemodialysis, peritoneal dialysis, and lipid dialysis (which removes lipid-soluble substances from the blood), as well as hemoperfusion (which more rapidly and efficiently clears specific poisons).

5.1. Non-Specific

Activated Charcoal

ATC code: A07BA01

Powder for oral liquid, 50 g, LOU 2

Indications and dose

Poisoning: Adsorbs a variety of drugs and chemicals (e.g., physical binding of a molecule to the surface of charcoal particles); desorption of bound particles may occur unless the ratio of charcoal to toxin is extremely high

Adult

Oral: 50 to 100 g as a single dose, as soon as possible after ingestion of poison, but it may still be effective up to 1 hour after ingestion of the poison or longer in the case of modified release (m/r) preparations or drugs with antimuscarinic (anticholinergic) properties; repeated doses are given after overdosage with carbamazepine, dapsone, phenobarbital, quinine, theophylline

Paediatric

Reduction of absorption of poisons, oral

Neonate, infant, or **child:** 1 g/kg (maximum 50 g) as a single dose as soon as possible after ingestion of poison

Active elimination of poisons, oral

Neonate, infant, or **child:** 1 g/kg (maximum 50 g) every 4 hours

Contraindications: Poisoning by hydrocarbons with high potential for harm if aspirated, poisoning by corrosive substances (may prevent visualization of lesions caused by poison), alcohols, malathion, cyanides, metal salts including iron and lithium salts. unprotected airway, GI tract (GIT) not intact, bowel obstruction.

Precautions: Drowsy or unconscious child (risk of aspiration (intubate before administration via nasogastric or gastric tube)), not effective for poisoning with alcohols, clofenotane (dicophane, dichlorodiphenyltrichloroethane [DDT]), cyanides, malathion, and metal salts including iron and lithium.

Renal impairment: Not absorbed, no dose adjustment necessary.

Hepatic impairment: Not absorbed, no dose adjustment necessary.

Adverse effects: Black stools, colicky abdominal pain, nausea, vomiting, constipation or diarrhoea, Bowel obstruction, aspiration, pneumonitis.

Interactions with other medicines: Acetylcysteine, acetylcysteine (antidote), citalopram, digoxin, methotrexate, theophylline, acarbose, leflunomide, miglitol

Notes:

- To be administered as soon as possible after ingestion if significant toxicity is anticipated, preferably within 1 hour for greatest effect.
- Administration after 1 hour is only of any potential benefit in selected poisonings.
- The powder should be mixed with fluid such as soft drinks, fruit juice, fruit syrup or chocolate syrup to mask the taste and form a drinkable solution. It should be Mixed well immediately prior to ingestion.
- It should not be mixed with milk or ice cream
- Child must drink slowly to reduce risk of vomiting.
- Palatability is improved by chilling.
- Drinking may be easier if mixture is covered or the child drinks with their eyes closed.
- Unconscious patients in whom decontamination is indicated require intubation

to protect their airway. Activated charcoal can be administered via an orogastric or nasogastric tube after aspiration of stomach contents. This route may also be used in conscious patients who refuse, or cannot take, oral charcoal.

» Laxatives should not be used concurrently with repeat dose activated charcoal because of the risk of fluid and electrolyte disturbances.

» Commonly used with sorbitol 25 g

5.2. Specific

Acetylcysteine

ATC code: V03AB23

Injection, 200 mg/mL in 10-mL amp, LOU 4

Indications and dose

Adult

Paracetamol overdosage, by IV infusion: Initially 150 mg/kg in 200 mL glucose 5% IV infusion over one hour, then 50 mg/kg in 500 mL glucose 5% IV infusion over 4 hours, then 100 mg/kg 1L glucose 5% IV infusions over 16 hours

Paracetamol overdosage, by oral (the injectable formulation may be administered orally): Loading dose: 140mg/kg, maintenance dose: 4 hours after loading dose, start 70mg/kg every 4 hours for a total of 17 doses. Repeat dose if emesis occurs within one hour of administration.

Paediatric

Paracetamol overdosage by IV infusion

Neonate, infant, or **child up to 5 years and body weight under 20 kg:** Initially 150 mg/kg in 3 mL/kg glucose 5% IV infusion given one hour , followed by 50 mg/kg in 7 mL/kg glucose 5% IV infusion given over 4 hours, then 100 mg/kg in 14 mL/kg glucose 5% IV infusion given over 16 hours

Child over 5 years or body weight over 20 kg: Initially 150 mg/kg in 100 mL glucose 5% intravenous infusion given one hour , followed by 50 mg/kg in 250 mL glucose 5% IV infusion given over 4 hours, then 100 mg/kg in 500 mL glucose 5% IV infusion given over 16 hours

Paracetamol overdosage, oral

Neonate, infant, or **child:** Initially 140 mg/kg, followed by 70 mg/kg every 4 hours for 17 doses, starting 4 hours after loading dose

Contraindications: There are no contraindications to acetylcysteine when used for paracetamol toxicity.

Precautions: Asthma (observe child carefully while slowly administering loading dose over 1–2 hours, do not delay treatment). Administered with or after a beta2 agonist to minimize the risk of bronchospasms.

Renal impairment: No dosage adjustment recommended.

Hepatic impairment: No dosage adjustment recommended.

Pregnancy: Safe to use

Adverse effects: hypersensitivity reactions including bronchospasm, angioedema, rashes and pruritis, hypotension or occasionally hypertension, nausea, vomiting, tachycardia, flushing.

Interactions with other medicines:

Nitroglycerin (minor).

Notes:

» Glucose solution, 5% is preferable infusion fluid.

» Continued infusion beyond 20 hours may be required in late presentations or repeated supratherapeutic ingestions if there is evidence of liver toxicity. In such cases, continue the final infusion rate until hepatic transaminases are falling.

» For oral therapy, all doses should be given even if paracetamol plasma level has dropped below toxic range.

» Repeat oral dose if vomiting occurs within 1 hour of administration.

» Emergency treatments such as antihistamines and H_2-blockers should be readily available in case of adverse effects.

» Hypersensitivity-like reactions may be managed by reducing infusion rate or suspending infusion until reaction has settled, specialist advice may be needed.

» Rash may be managed with an antihistamine, for example chlorpheniramine.

» Acute asthma may be managed with a short-acting beta$_2$-agonist such as salbutamol.

» The injectable may be administered orally.

Atropine

ATC code: A03BA01

Injection, 1 mg (as sulphate) in 1-mL amp, LOU 2

Indications and dose

Adult

Treatment of cholinergic effects associated with organophosphate or carbamate poisoning by IM or IV injection (depending on severity of poisoning): Initial dose of 1–2 mg for mild poisoning, and up to 6 mg for severe poisoning, every 5–10 minutes until the secretions are minimal, ventilation is adequate, skin becomes flushed and dry, pupils dilate, and tachycardia develops.

Treatment should be repeated if muscarinic symptoms reappear. In moderate to severely poisoned adults, atropine is given for at least 2 days. In severe cases atropine therapy should be withdrawn gradually to avoid abrupt recurrence of symptoms (e.g., pulmonary oedema).

Paediatric

Organophosphate or carbamate poisoning by IM or IV injection

Infant or **child:** 20 micrograms/kg (maximum dose 2 mg) every 5–10 minutes (depending on the severity of poisoning) until the skin becomes flushed and dry, pupils dilate, and tachycardia develops; dose may be repeated every 1–4 hours for at least 24 hours to maintain atropine effect.

Contraindications: Primary glaucoma or predisposition to narrow anterior chamber angle glaucoma, known hypersensitivity to atropine or other anticholinergic agents.

Precautions: Patients with obstructive disease of the GIT (e.g., pyloroduodenal stenosis, achalasia), cardio spasm, paralytic ileus or intestinal atony (especially in geriatric or debilitated patients), Reflux esophagitis, Severe ulcerative colitis or megacolon complicating ulcerative colitis, Prostatic enlargement, Unstable cardiovascular status in acute hemorrhage, Tachycardia secondary to cardiac insufficiency or thyrotoxicosis, Toxemia of pregnancy, Obstructive uropathy (e.g., bladder neck obstruction caused by prostatic hypertrophy), Myasthenia gravis (unless used to treat the adverse effects of an anticholinesterase agent), Due to risk of provoking hyperpyrexia due to reduced sweating, Atropine should not be given to febrile patients, or when the ambient temperature is high, Down syndrome

Renal impairment: Use with caution. No dosage adjustment necessary.

Hepatic impairment: Use with caution. No dosage adjustment necessary.

Pregnancy: Category A: No increase in the frequency of malformations or other direct or indirect harmful effects on the foetus have been observed, the safety of Atropine in pregnancy has not been positively established.

Breastfeeding: Should only be administered to breastfeeding mothers if absolutely necessary. Atropine may cause antimuscarinic effects in the infant. Atropine may inhibit breastfeeding.

Adverse effects: Dry mouth, blurred vision, photophobia, flushing and dryness of skin, rash, difficulty in micturition, constipation, arrhythmias, tachycardia, palpitations, fever, Nausea, vomiting, confusion, Closed-angle glaucoma, seizures.

Interactions with other medicines: Amitriptyline, chlorpheniramine, chlorpromazine, haloperidol, metoclopramide, neostigmine, pyridostigmine

Notes:

» Administer undiluted via rapid IV injection as slow injection may result in paradoxical bradycardia.

Calcium Folinate (Calcium Leucovorin, Folinic Acid or Leucovorin)

ATC code: V03AF03

Injection, 10 mg/mL (5-mL vial), LOU 4

Indications and dose

Reduction of methotrexate-induced toxicity associated with high-dose methotrexate therapy (folate rescue); usually started 24 hours after beginning the methotrexate infusion; doses and length of treatment may be based on methotrexate concentration

Adult

Antidote to methotrexate (usually started 12 to 24 hours after administration of methotrexate), by IM or IV injection or IV infusion: Up to 120 mg in divided doses over 12–24 hours, then 12–15 mg by IM injection, or 15 mg by mouth every 6 hours for 48–72 hours

Methotrexate overdosage (started as soon as possible, preferably within 1 hour of administration of methotrexate), by IV injection or infusion: Dose equal to or higher than that of methotrexate, at rate not exceeding 160 mg/min

Paediatric

Antidote to methotrexate (usually started 12 to 24 hours after administration of methotrexate) by IM or IV injection or IV infusion

Up to 120 mg in divided doses over 12–24 hours, then 12–15 mg by *IM injection*, or 15 mg *oral* every 6 hours for 48–72 hours.

Methotrexate overdosage (started as soon as possible, preferably within 1 hour of administration of methotrexate) by IV injection or infusion

Dose equal to or higher than that of methotrexate, at rate not exceeding 160 mg/min

Contraindications: Pernicious anaemia or other megaloblastic anaemias due to vitamin B_{12} deficiency

Precautions: Avoid simultaneous administration of methotrexate, Intrathecal administration is contraindicated

Renal impairment and Hepatic impairment: Dose reduction not necessary.

Adverse Effects: Allergic reactions, fever, seizures, fainting.

Interactions with other medicines: Phenobarbital, phenytoin, fluorouracil, trimethoprim

Calcium Gluconate

ATC code: A12AA03

Injection, 100 mg/mL in 10-mL amp, LOU 3

Indications and dose

Adult

Magnesium toxicity, severe hyperkalaemia not due to digoxin toxicity, acute hypocalcaemia (including hypocalcaemia caused by ethylene glycol toxicity, hydrofluoric acid ingestion, and oxalate poisoning), CCB toxicity, topical treatment of hydrofluoric acid burns, by slow IV injection: 1 g (2.2 mmol); in hypocalcaemic tetany, this is followed by about 4 g (8.8 mmol) daily by continuous IV infusion

Cardiotoxicity in presence of hypercalcaemia, hypocalcaemia, or hypomagnesemia by slow IV injection: 1.5–3 g over 2–5 minutes

Paediatric

Urgent correction of acute hypocalcaemia, hyperkalaemia or hypermagnesaemia, CCB toxicity, by slow IV

Neonate, infant, or **child:** 50 mg/kg as a single dose; maximum dose 200 mg (20 mL); repeat dose after 10 minutes if necessary; if ineffective, consider IV infusion.

Maintenance correction of acute hypocalcaemia, hyperkalaemia or hypermagnesaemia, maintenance treatment of CCB toxicity, continuous IV infusion

Neonate: 200 mg/kg daily over 24 hours, adjusted to response

Infant or **child under 2 years**: 500 mg/kg daily (usual maximum 4 g) over 24 hours

Child over 2 years: 4 g over 24 hours

Hydrofluoric acid burns, topical

Child, all ages: Apply 2.5% calcium gluconate gel to the affected area for at least 30 minutes, usually longer

Contraindications: There are no contraindications to the use of calcium gluconate for treatment of toxicity or poisoning.

Precautions: Conditions associated with hypercalcaemia and hypercalciuria, digoxin therapy, renal impairment.

Renal impairment: Moderate to severe impairment: may require dosage adjustment depending on calcium level. Risk of hypercalcaemia and renal calculi.

Hepatic impairment: No dosage adjustment necessary.

Adverse effects: GI disturbances, constipation, injection site reactions, fall in blood pressure, bradycardia, arrhythmia, peripheral vasodilation. Renal calculi, severe tissue damage with extravasation.

Interactions with other medicines: Ciprofloxacin, digoxin, hydrochlorothiazide, levothyroxine, ofloxacin

Notes:

- For IV infusion, should be diluted to 20 mg/mL with glucose 5% or sodium chloride 0.9%.
- Maximum administration rate is 20 mg/kg/hour (or 10 mg/kg/hour in neonates).
- IV injection should be administered via slow IV injection over 5–10 minutes.
- Avoid extravasation, should not be given by IM or SC injection.
- Continuous ECG monitoring is recommended during IV calcium administration.
- Significant hydrofluoric acid poisoning (> 3% of BSA) may result in marked systemic hypocalcaemia requiring IV therapy.
- To extemporaneously prepare 2.5% calcium gluconate gel, 2.5 mL (250 mg) of injection solution should be combined with 100 mL of water soluble lubricant.

Deferasirox

ATC code: V03AC03

Tablet, 100 mg, 400 mg, LOU 4

Indications and dose

Adult

Transfusion-related chronic iron overload in patients with beta thalassaemia major who receive frequent blood transfusions (7 mL/kg/month or more of packed red blood cells), oral: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood, then adjusted in steps of 3.5–7 mg/kg every 3–6 months; maintenance dose adjusted according to serum-ferritin concentration, maximum 28 mg/kg per day, usual maximum 21 mg/kg

Transfusion-related chronic iron overload when desferrioxamine is contraindicated or inadequate in patients with beta thalassaemia major who receive infrequent blood transfusions (<7 mL/kg/month of packed red blood cells); transfusion-related chronic iron overload when desferrioxamine is contraindicated or inadequate in patients with other anaemias, oral: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood, then adjusted in steps of 3.5–7 mg/kg every 3–6 months, maintenance dose adjusted according to serum-ferritin concentration, maximum 28 mg/kg per day, usual maximum 21 mg/kg

Chronic iron overload when desferrioxamine is contraindicated or inadequate in non-transfusion-dependent thalassaemia syndromes, oral: Initially 7 mg/kg once daily, then adjusted in steps of 3.5–7 mg/kg every 3–6 months, maintenance dose adjusted according to serum-ferritin concentration and liver-iron concentration; maximum 14 mg/kg per day

Paediatric

Transfusion-related chronic iron overload when desferrioxamine is contraindicated or inadequate in patients with beta thalassaemia major who receive frequent blood transfusions (7 mL/kg/month or more of packed red blood cells), oral

Child 2–5 years: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood, then adjusted in steps of 3.5–7 mg/kg every 3–6 months; maintenance dose adjusted according to serum-ferritin concentration; maximum 28 mg/kg per day, usual maximum 21 mg/kg

Transfusion-related chronic iron overload in patients with beta thalassaemia major who receive frequent blood transfusions (7 mL/kg/month or more of packed red blood cells), oral

Child 6–17 years: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood, then adjusted in steps of 3.5–7 mg/kg every 3–6 months; maintenance dose adjusted according to serum-ferritin concentration; maximum 28 mg/kg per day, usual maximum 21 mg/kg

Transfusion-related chronic iron overload when desferrioxamine is contraindicated or inadequate in patients with beta thalassaemia major who receive infrequent blood transfusions (<7 mL/kg/month of packed red blood cells); transfusion-related chronic iron overload when desferrioxamine is contraindicated or inadequate in patients with other anaemias, oral

Child 2–17 years: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood, then adjusted in steps of 3.5–7 mg/kg every 3–6 months; maintenance dose adjusted according to serum-ferritin concentration, maximum 28 mg/kg per day, usual maximum 21 mg/kg

Chronic iron overload when desferrioxamine is contraindicated or inadequate in non-transfusion-dependent thalassaemia syndromes, oral

Child 10–17 years: Initially 7 mg/kg once daily, maintenance dose adjusted according to serum-ferritin concentration and liver-iron concentration; maximum 7 mg/kg per day

Contraindications: None

Precautions

Elderly (increased risk of adverse effects), history of liver cirrhosis, not recommended in conditions which may reduce life expectancy (e.g., high risk myelodysplastic syndromes), platelet count less than $50x10^9$/L, risk of GI ulceration and haemorrhage, unexplained cytopenia—consider treatment interruption

Hepatic impairment: reduce initial dose considerably then gradually increase to max. 50%of normal dose in moderate impairment: avoid in severe impairment

Renal impairment: use with caution in patients with serum creatinine levels above normal range. Caution should especially be used in patients with CrCl between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections

Pregnancy: avoid unless essential.

Breastfeeding: avoid.

Adverse effects: Constipation, diarrhoea, GI discomfort, headache, nausea, skin reactions, urine abnormalities, vomiting, anxiety, cataract, cholelithiasis, dizziness, fatigue, fever, GI disorders, GI haemorrhage (including fatal cases), hearing impairment, hepatic disorders, laryngeal pain, maculopathy, oedema, renal tubular disorders, sleep disorder, optic neuritis, SCARs, acute kidney injury, alopecia, anaemia aggravated, hyper-ammonaemic encephalopathy, hypersensitivity vasculitis, lens opacity, leucopenia, metabolic acidosis, nephritis tubulointerstitial, nephrolithiasis, neutropenia, pancreatitis acute, pancytopenia, renal tubular necrosis, thrombocytopenia

Interactions with other medicines: Aminophylline, antacids (aluminium hydroxide), antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone), aspirin (high dose), bisphosphonates, clozapine, corticosteroids, protease inhibitors (ritonavir), pioglitazone, repaglinide, rifampicin, taxanes (paclitaxel), theophylline

Notes

» Monitoring of the following patient parameters: baseline serum creatinine twice and CrCl once before initiation of treatment, weekly in the first month after treatment initiation or modification, then monthly thereafter, proteinuria before treatment initiation then monthly thereafter, and other markers of renal tubular function as needed, liver function before treatment initiation, every 2 weeks during the first month of treatment, then monthly thereafter, eye and ear examinations before treatment and annually during treatment, serum-ferritin concentration monthly.

» Monitor liver-iron concentration every three months in children with non-transfusion dependent thalassaemia syndromes when serum ferritin is 800 micrograms/L.

» Monitor body weight, height, and sexual development before treatment and then annually thereafter.

Tablets may be crushed and sprinkled on to soft food (yoghurt or apple sauce), then administered immediately.

Deferoxamine (Desferrioxamine)

ATC code: V03AC01

Powder for injection, 500 mg (as mesilate) in vial, LOU 4

Indications and dose

Adult

Acute iron poisoning, by slow IV infusion: Initially 15 mg/kg/hour, reduced after 4–6 hours so that total dose does not exceed 80 mg/kg in 24 hours

Chronic iron overload, *by SC or IV infusion*: Lowest effective dose (usually within range of 20–60 mg/kg/day) 4–7 days a week

Aluminium overload in end-stage renal failure, by IV infusion: 5 mg/kg, once a week during last hour of dialysis; diagnosis of iron overload, by IM injection, 500 mg

Diagnosis of aluminium overload, by IV infusion: 5 mg/kg during last hour of dialysis

Paediatric

The preferred route of administration is IV.

Acute iron poisoning, slow IV infusion

Neonate, infant, or **child:** Initially 15 mg/kg/hour, reduced after 4–6 hours so that total dose does not exceed 80 mg/kg in 24 hours; maximum dose 6 g/day

Acute iron poisoning, by IM

50 mg/kg/dose every 6 hours; maximum dose 6 g/day

Note: More than 24 hours of therapy are required for acute iron overdose. Therapeutic endpoints to cease infusion are poorly defined but may be indicated by clinically stable patient and serum iron < 60 micromol/L.

Chronic iron overload, SC or IV infusion:

Infant or **child:** Initially up to 30 mg/kg over 8–12 hours, on 3–7 days per week; for established iron overload, the dose is usually between 20 and 50 mg/kg daily; the dose should reflect the degree of iron overload; use the lowest effective dose

Diagnosis of iron overload, by IM

Child: 500 mg

Precautions: Renal impairment, eye and ear examinations before and at 3-month intervals during treatment are necessary to assess toxicity, aluminium encephalopathy (may exacerbate neurological dysfunction), for all children monitor body weight and

height at 3-month intervals (risk of growth restriction with excessive doses).

Hepatic impairment: No dosage adjustment necessary.

Renal impairment: Metal complexes excreted by kidneys (in severe renal impairment dialysis increases rate of elimination).

Adverse effects: Injection site reactions including redness, pain, swelling, rashes and itch, hypotension (especially when given too rapidly by IV injection), fever, arthralgia, myalgia, rash, anaphylactoid reactions, Renal failure, non-cardiogenic pulmonary oedema, disturbances of hearing and vision (including lens opacity and retinopathy), Anaphylaxis, acute respiratory distress syndrome, neurological disturbances

Chronic use - Growth retardation, bone deformities (both with high doses), Neurosensory deafness, Bone marrow depression, ocular toxicity, mucormycosis and other unusual infections.

Interactions with other medicines: There are no known significant interactions for which it is recommended to avoid concomitant use.

Notes:

- For IV or SC infusion, reconstitute powder with water for injection to a concentration of 100 mg/mL. Dilute with glucose 5% or sodium chloride 0.9%.
- For IM or SC administration, reconstitute powder with water for injection to a concentration of 100 mg/mL. No further dilution required.
- For all children, monitor body weight and height at 3-month intervals (risk of growth restriction with excessive doses).
- Iron excretion induced by deferoxamine is enhanced by ascorbic acid and ascorbic acid is sometimes prescribed for this purpose.

Ethanol

ATC code: V03AZ01

Injection, 100% in 10-mL amp, LOU 4

Oral liquid (medicinal, 95–96% [1 mL, 5 mL]), LOU 4

Indications and dose

Used to manage toxicity due to ingestion of methanol or ethylene glycol

Adult

IV: Initial 600 to 700 mg/kg (7.6–8.9 mL/kg) using a 10% solution; goal is to maintain serum ethanol levels above 100 mg/dL

Oral: Initial 600 to 700 mg/kg (7.6–8.9 mL/kg) using a 98% solution

Notes for oral: Dilute solution to ≤20% to reduce risk of gastritis; must be administered precisely at 60-minute intervals.

Dose adjustment for hemodialysis

- IV: 169 mg/kg/hour equivalent to 2.13 mL/kg/hour using a 10% solution
- Oral: 169 mg/kg/hour equivalent to 0.22 mL/kg/hour using a 98% solution

Paediatric

Reduce ethanol loading dose if methanol or ethylene glycol ingested with alcohol; may need to increase ethanol maintenance dose in patients with chronic alcohol consumption

Loading dose (oral)

95% EtOH: 0.8–1 mL/kg

40% EtOH (80 proof undiluted liquor): 2 mL/kg

43% EtOH (86 proof undiluted liquor): 1.8 mL/kg

Maintenance dose (oral)

43% EtOH: 0.1 mL/kg/hour

95% EtOH: 0.1 mL/kg/hour

IV dose (10% EtOH)

10% EtOH = 7.9 g/dL

Loading: 8–10 mL/kg IV, not to exceed 200 mL

Maintenance: 0.83 mL/kg/hour IV (IV)

10% EtOH = 7.9 g/dL

40% EtOH (80 proof undiluted liquor) = 31.6 g/dL

43% EtOH (86% proof undiluted liquor) = 34 g/dL

95% EtOH (absolute alcohol) = 75 g/dL

Continue maintenance dose until methanol or ethylene glycol levels are below 10 mg/dL.

Contraindications: Hypersensitivity, Seizure disorder, Diabetic coma, Subarachnoid injection of dehydrated alcohol in patients receiving anticoagulants

Precautions: Caution in diabetes mellitus, gout patients, hepatic impairment, shock

Pregnancy: Use ethanol (injection) with caution during pregnancy if benefits outweigh risks.

Breastfeeding: Ethanol enters breast milk, use with caution

Adverse effects: Intoxication, low blood pressure (hypotension) with flushing, agitation, low blood sugar (hypoglycemia), nausea, vomiting, excessive urination

Fomepizole

ATC code: V03AB34

Injection, 5 mg/mL (as sulphate) in 20-mL amp, LOU 5

Indications and dose

Adult

Used to treat poisoning by ethylene glycol or methyl alcohol, which are converted to toxic metabolites by alcohol dehydrogenase.

Given in a loading dose of 15 mg/kg followed by 10 mg/kg every 12 hours for 4 doses; the dose should then be increased to 15 mg/kg every 12 hours until serum concentrations of ethylene glycol or methyl alcohol are <20 mg per 100 mL. **All doses should be given by IV infusion over 30 minutes in at least 100 mL of sodium chloride 0.9% or glucose 5%.**

- In patients who also require haemodialysis, give every 4 hours during haemodialysis sessions.

Paediatric: Consult product literature

Precautions: Pophyria

Adverse Effects: headache, nausea, dizziness, drowsiness, and taste disturbances. Other less common adverse effects include abdominal or back pain, fever, rash and other hypersensitivity reactions, GI disturbances, hypotension, tachycardia or bradycardia, shock, anuria, multi-organ system failure, disseminated intravascular coagulation, anaemia, lymphangitis, pharyngitis, and hiccups. Nervous system reactions include seizures, lightheadedness, agitation, anxiety, vertigo, flushing, nystagmus, abnormal smell, and speech or visual disturbances, injection site reactions, Transient increases in hepatic enzyme values and eosinophilia

Interactions with other medicines: Alcohol

Flumazenil

ATC code: V03AB25

Injection, 100 micrograms/mL (5-mL amp), LOU 4

Indications and dose

Adult

Reversal of sedative effects of benzodiazepines in anaesthesia and clinical procedures, by IV injection: 200 micrograms, dose to be administered over 15 seconds, then 100 micrograms every 1 minute if required; usual dose 300–600 micrograms, maximum 1 mg per course

Reversal of sedative effects of benzodiazepines in intensive care, by IV injection: 300 micrograms, dose to be administered over 15 seconds, then 100 micrograms every 1 minute if required, maximum 2 mg per course

Reversal of sedative effects of benzodiazepines in intensive care (if drowsiness recurs after injection): Initially by IV infusion, 100–400 micrograms/hour, adjusted according to response; alternatively by IV injection 300 micrograms, adjusted according to response

Paediatric

Reversal of sedative effects of benzodiazepines, by IV injection

Neonate: 10 micrograms/kg every 1 minute, dose to be administered over 15 seconds

Child: 10 micrograms/kg every 1 minute (max. per dose 200 micrograms); dose to be administered over 15 seconds, maximum 1 mg per course, maximum 50 micrograms/kg per course

Reversal of sedative effects of benzodiazepines (if drowsiness recurs after injection), by IV infusion

Neonate: 2–10 micrograms/kg/hour, adjusted according to response

Child: 2–10 micrograms/kg/hour (max. per dose 400 micrograms/hour), adjusted according to response

Reversal of sedative effects of benzodiazepines in intensive care, by IV injection

Child: 10 micrograms/kg every 1 minute (max. per dose 200 micrograms), dose to be administered over 15 seconds, maximum 2 mg per course, maximum 50 micrograms/kg per course

Precautions

- Flumazenil should only be administered by, or under the direct supervision of, personnel experienced in its use
- Avoid rapid injection following major surgery
- Avoid rapid injection in high-risk or anxious patients
- Benzodiazepine dependence may precipitate withdrawal symptoms
- Children - ensure neuromuscular blockade cleared before giving
- Head injury - rapid reversal of benzodiazepine sedation may cause convulsions
- History of panic disorders - risk of recurrence
- Prolonged benzodiazepine therapy for epilepsy - risk of convulsions
- Short-acting - repeat doses may be necessary. Benzodiazepine effects may persist for at least 24 hours

Adverse effects: Anxiety, diplopia, dry mouth, eye disorders, flushing, headache, hiccups, hyperhidrosis, hyperventilation, hypotension, insomnia, nausea, palpitations, paraesthesia, speech disorder, tremor, vertigo, vomiting, abnormal hearing, arrhythmias, chest pain, chills, cough, dyspnoea, nasal congestion, seizure (more common in patients with epilepsy), withdrawal syndrome

Notes: For continuous IV infusion, dilute with glucose 5% or sodium chloride 0.9%

Lipid Emulsion

ATC code: B05BA02

Injection, 20% in 200 mL to 500 mL measure, LOU 4

Indications and dose

Adult

IV lipid emulsion therapy (also known as lipid resuscitation therapy) is the current recommended treatment for local anesthetic systemic toxicity (LAST). It is also recommended as an adjunct to advanced cardiac life support measures in suspected LAST-induced cardiac arrest.

It may be used for many other acute toxicities and poisonings. Drug classes that have been investigated include tricyclic antidepressants, CCBs, beta-blockers, antipsychotics, insecticides, and organophosphates. Specific drugs also studied include bupropion, lamotrigine, cocaine, and diphenhydramine.

Patients under 70 kg: Rapid 1.5 mL/kg (of lean body weight) bolus of 20% lipid emulsion followed by a 0.25 mL/kg/min infusion.

Note: The same bolus dose is repeatable, along with doubling the infusion rate if cardiovascular instability continues. The recommended dosing limit is approximately 12 mL/kg.

Paediatric: Consult product literature

Contraindications: Severe disorders of fat metabolism such as in severe liver damage and acute shock

Precautions: Fat overload syndrome may occur, usually reversible upon discontinuation.

Adverse effects: Cholestasis, increase in blood bilirubin, cytolytic hepatitis, cholecystitis, abnormalities in liver function tests, increase in pancreatic enzymes

Naloxone

ATC code: V03AB15

Injection, 400 micrograms/mL (HCl) in 1-mL amp, LOU 4

Indications and dose

Adult

Overdosage of opioids, by IV injection: 0.4–2 mg repeated at intervals of 2–3 minutes up to a maximum of 10 mg; review diagnosis if respiratory function does not improve

Note: Naloxone HCl may be administered in the same doses by IM or SC injection, but only if the IV route is not feasible (slower onset of action).

Overdosage of opioids, by continuous IV infusion using an infusion pump: 10 mg diluted in 50 mL glucose IV infusion solution 5% at a rate adjusted according to response (initial infusion rate may be set to deliver 60% of IV dose [see above] over 1 hour)

Paediatric

Opioid overdosage, IV

Neonate, infant, or **child:** 10 micrograms/kg, if no response give subsequent dose of 100 micrograms/kg; review diagnosis if respiratory function does not improve; further doses may be required if respiratory function deteriorates.

Note: Naloxone HCl may be administered in the same doses by IM or SC injection, but only if the IV route is not feasible (slower onset of action).

Continuous IV infusion using an infusion pump

Neonate, infant, or **child:** 5–20 micrograms/kg/hour, adjusted according to response

Contraindications: There are no contraindications to use of naloxone for treatment of opioid toxicity.

Precautions: Physical dependence on opioids or other situations where acute withdrawal syndrome may be precipitated, cardiovascular disease, postoperative patients (may reverse analgesia and increase blood pressure).

Hepatic impairment: No dose adjustment necessary.

Renal impairment: Excretion of some opioids and/or their active metabolites (codeine, dextropropoxyphene, dihydrocodeine, morphine, pethidine, oxycodone) is delayed in impairment and they will accumulate, extended treatment with naloxone infusion may be required to reverse opioid effect.

Adverse effects: Nausea, vomiting, sweating, tachycardia, ventricular arrhythmias, Cardiac arrest.

Interactions with other medicines: There are no known interactions for which it is advised to avoid concomitant use.

Notes:

- For continuous IV infusion, diluted to a concentration of 4 micrograms/mL with glucose 5% or sodium chloride 0.9%.
- For IV bolus, administered over 30 seconds as undiluted preparation.
- IV dose may be repeated every 2–3 minutes until response.
- After initial response, IV dose may need to be repeated every 20–60 minutes due to short duration of action.
- Naloxone should not be given to neonates of mothers who have been taking methadone or heroin.

Phytomenadione (Vitamin K_1, Phytonadione)

ATC code: B02BA01

Injection, 10 mg/mL in 1-mL amp. LOU 4

Indications and dose

Adult

Antagonist to warfarin, warfarin-induced hypoprothrombinaemia, no bleeding or minor bleeding, by slow IV injection: 500 micrograms; oral, up to 5 mg

Moderate haemorrhage, oral or by IM injection: 10–20 mg

Severe haemorrhage, by slow IV injection: 5–10 mg

Paediatric

Reversal of coumarin anticoagulation when continued anticoagulation required or if no significant bleeding by IV injection

Child: 15–30 micrograms/kg (max. per dose 1 mg) for 1 dose, repeat as necessary

Reversal of coumarin anticoagulation when anticoagulation not required or if significant bleeding by IV injection

Child: 250–300 micrograms/kg (max. per dose 10 mg) for 1 dose

Precautions: IV injections should be given very slowly (risk of vascular collapse)

Hepatic impairment: Higher doses may be required for adequate response.

Renal impairment: Dose reduction not necessary.

Adverse effects: Hypersensitivity reactions including flushing, dyspnoea, bronchospasm, dizziness, hypotension and respiratory or circulatory collapse which may be due to polyethoxylated castor oil surfactant in some injection formulations, rather than due to phytomenadione.

Interactions with other medicines (*indicates serious): *Warfarin

Notes:

- In infants with cholestatic disease, vitamin K must be given either intramuscularly or intravenously because oral absorption is likely to be impaired.
- IV preparations can usually be given orally. Please check specific product information.

Pralidoxime

ATC code: V03AB04

Powder for injection, 1 g (as chloride of mesylate) vial, LOU 4

Indications and dose

Adult

Adjunct to atropine in the treatment of poisoning by organophosphorus insecticide or nerve agent, by IV infusion: Initially 30 mg/kg to be given over 20 minutes, followed by 8 mg/kg/hour, maximum 12 g per day

Antimyasthenic overdose: Initial dose of pralidoxime chloride 1 to 2 g is given by IV infusion, followed by an IV infusion of 0.5 to 1 g/hour; alternatively, the initial dose can be repeated after 1 hour and then every 3 to 8 hours if needed

» Renal impairment: Dose may need to be reduced

Paediatric

Adjunct to atropine in the treatment of poisoning by organophosphorus insecticide or nerve agent by IV infusion: Initially 30 mg/kg, to be given over 20 minutes, followed by 8 mg/kg/hour, maximum 12 g per day

Contraindications Poisoning with carbamates, poisoning with organophosphorus compounds without anticholinesterase activity

Precautions: Myasthenia gravis

Renal impairment Use with caution.

Adverse effects: Dizziness, drowsiness, headache, hyperventilation, muscle weakness, nausea, tachycardia, vision disorder

Notes:

» The loading dose may be administered by IV injection (diluted to a concentration of 50 mg/mL with water for injections) over at least 5 minutes if pulmonary oedema is present or if it is not practical to administer an IV infusion.

» In children, For IV infusion, each vial should be reconstituted with 20 mL water for injections, then diluted to a concentration of 10–20 mg/mL with sodium chloride 0.9%.

» In the treatment of organophosphorus poisoning, pralidoxime should be given as soon as possible. After about 36 hours it becomes less effective since cholinesterase inactivation usually becomes irreversible after this time, however, patients with severe poisoning may occasionally respond up to 48 hours or longer after exposure, depending on the organophosphate involved.

Protamine

ATC code: V03AB14

Injection, 10 mg/mL (as a sulphate) in 5-mL amp, LOU 4

Indications and dose

Adult

Heparin overdose, by IV injection over approximately 10 minutes: 1 mg neutralizes 80–100 IU heparin sodium when given within 15 minutes; if more time has elapsed, less protamine is needed as heparin is rapidly excreted.

Paediatric

Heparin overdose by IV injection or IV infusion

Child 1 month–12 years: 1 mg of protamine neutralizes approximately 100 units of heparin if <30 minutes has elapsed since overdose, 500–750 micrograms if 30–60 minutes has elapsed, 375–500 micrograms if 60–120 minutes has elapsed, 250–375 micrograms if over 120 minutes has elapsed; maximum dose 50 mg; do not exceed a rate of 5 mg/min.

Heparin overdose, by SC injection

Child 1 month–12 years: 1 mg neutralizes approximately 100 units of heparin; give 50–100% of the total dose by IV injection (rate not exceeding 5 mg/min), then give any remainder of the dose by IV infusion over 8–16 hours; maximum total dose 50 mg

Precautions: If used in excess, protamine has an anticoagulant effect, allergic reactions increased in persons at risk including previous treatment with protamine or protamine insulin, fish allergies, rapid administration or high dose.

Hepatic and renal impairment: Dose reduction not necessary.

Adverse effects: Nausea, vomiting, lassitude, flushing, hypotension/hypertension, Bradycardia, dyspnoea, allergic reactions (including angioedema, anaphylaxis), cardiovascular collapse, pulmonary vasoconstriction/hypertension.

Interactions with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

» 1 mg neutralizes approximately 100 units of unfractionated heparin when given within 15 minutes, if longer time, less protamine is needed as heparin is rapidly excreted.

» Activated partial thromboplastin time (APTT) or other appropriate blood clotting parameters should be monitored.

» Not to be administered at a rate exceeding 5 mg/min.

» May be diluted, if necessary, with sodium chloride 0.9%.

Sodium Hydrogen Carbonate (Sodium Bicarbonate, Sodium Acid Carbonate, Nahco3)

ATC code: B05XA02

Injectable solution 8.4% in 10-mL amp (equivalent to Na+ 1000 mmol/L, HCO3- 1000 mmol/L), LOU 4

Indications and dose

Adult

Metabolic acidosis: Slow IV injection of a strong solution (up to 8.4%) or continuous IV infusion of a weaker solution (usually 1.4%), an amount appropriate to the body base deficit (see notes).

Paediatric

Severe metabolic acidosis IV (by continuous infusion with 1.4% solution co-infused with isotonic sodium chloride, or by slow infusion of 8.4% solution)

Neonate, infant, or **child:** mmol of HCO_3 = 0.5 × weight (kg) × (24 – serum mmol of HCO_3/L); half the required volume of sodium hydrogen carbonate solution should be infused and the patient's clinical progress and serum HCO_3 should be monitored before giving the remaining half.

1.4% solution contains, per 1 mL, 0.167 mmol of Na and 0.167 mmol of HCO_3.

8.4% solution contains, per 1 mL, 1 mmol of Na and 1 mmol of HCO_3.

If acid–base status not available, IV infusion

Child over 2 years: 1–5 mmol/kg; subsequent doses should be based on patient's acid–base status; extreme care should be taken when administering to patients without confirmed metabolic acidosis.

Contraindications: Metabolic or respiratory alkalosis, hypocalcaemia, hypochlorhydria, hypernatraemia, unknown abdominal pain, inadequate ventilation during cardiopulmonary resuscitation, excessive chloride losses. Not for intra-arterial or intra-osseous injection.

Precautions: Restrict intake in impaired renal function, congestive heart failure, hypertension, peripheral and pulmonary oedema, other sodium-retaining conditions.

Caution should be taken when administering to patients under 2 years as hypernatraemia due to rapid injection may occur. Maximum rate in children under 2 should be 10 mmol/min.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Severe: avoid, specialized role in some forms of renal disease.

Adverse effects: Excessive administration may cause hypokalaemia and metabolic alkalosis, especially in renal impairment, large doses may give rise to sodium accumulation and oedema. Extravasation may lead to tissue necrosis or ulceration.

Interactions with other medicines (*indicates serious): Epinephrine, *flecainide, quinine

Notes:

- Monitor for hypokalaemia and hyperkalaemia.
- Na+ content = 1 mmol/mL (8.4%) and HCO_3- 1 mmol/mL (8.4%).
- 0.18 mmol/mL ≈ 1.5% ≈ isotonic.
- Rapid injection (10 mL/min) of sodium hydrogen carbonate solutions in children up to 2 years of age may produce hypernatraemia, decreased cerebrospinal fluid pressure and possible intracranial haemorrhage.
- Avoid extravasation, may cause cellulitis and tissue necrosis due to the hypertonicity of sodium hydrogen carbonate. Preferably administer into a large vein.

Sodium Nitrite

ATC code: V03AB08

Injection, 30 mg/mL in 10-mL amp, LOU 4

Indications and dose

Adult

Poisoning with cyanides (used in conjunction with sodium thiosulphate): The usual dosage regimen is 300 mg of sodium nitrite (10 mL of a 3% solution) given intravenously over 2 to 20 minutes followed by 12.5 g of sodium thiosulphate (50 mL of a 25% solution or 25 mL of a 50% solution) given intravenously over 10 minutes. The methaemoglobin concentration should not be allowed to exceed 30 to 40%.

Paediatric

Poisoning with cyanides (used in conjunction with sodium thiosulphate)

Child 1 month to 18 years: 4 to I 0 mg/kg to a maximum of 300 mg (0.13 to 0.33 mL/kg of a 3% solution; maximum 10 mL) by IV injection over 5 to 20 minutes, followed by sodium thiosulphate 400 mg/kg to a maximum of 12.5 g (as a 25 or 50% solution) by IV injection over 10 minutes.

Precautions:

- Blood pressure should be monitored when giving sodium nitrite as rapid injection can cause hypotension. It should be used cautiously with other drugs that reduce blood pressure or volume, or that cause vasodilatation, such as antihypertensives, diuretics, and phosphodiesterase type-5 inhibitors.
- Carcinogenicity. Sodium nitrite is a precursor for the formation of N-nitroso compounds such as nitrosamines, many of which are carcinogenic in animals. Occupational exposure to sodium nitrite has been associated with a higher incidence of oesophageal cancer.
- Severe methaemoglobinaemia has been reported after consumption of nitrite-contaminated meat

Renal impairment: Sodium nitrite is excreted by the kidneys and care is needed.

Adverse Effects: Sodium nitrite may cause nausea and vomiting, abdominal pain, dizziness, headache, cyanosis, tachypnoea, and dyspnoea. Blurred vision, confusion, anxiety, diaphoresis, fatigue, and generalised numbness or tingling have also been reported. Vasodilatation has resulted in syncope, hypotension, and tachycardia, arrhythmias, cardiovascular collapse, coma, convulsions, and death have occurred in overdose.

Notes

- Sodium nitrite has also been suggested in the treatment of hydrogen sulfide poisoning.
- Sodium nitrite is used as a rust inhibitor, for example in instrument disinfectants. It is also used as a preservative in foods such as cured meats.
- Sodium nitrite generates nitric oxide and is

being investigated for the treatment of vaso-occlusive crisis in sickle-cell disease, myocardial ischaemic-reperfusion injury, and cerebral vasospasm.

» Neonates and infants under 6 months of age may be particularly susceptible to methaemoglobinaemia with sodium nitrite.

Sodium Thiosulphate

ATC code:-V03AB06

Injection, 250 mg/mL in 50-mL amp, LOU 4

Indications and dose

Adult

Cyanide poisoning: 300 mg of sodium nitrite (10 mL of a 3% solution) given intravenously over 2 to 20 minutes followed by 12.5 g of sodium thiosulphate (50 mL of a 25% solution or 25 mL of a 50% solution) given intravenously over 10 minutes; if symptoms of cyanide toxicity recur, it has been suggested that the injections of nitrite and thiosulphate may be repeated after 30 minutes at half the initial doses.

Paediatric

Cyanide poisoning

Child 1 month to 18 years: Sodium nitrite 4 to 10 mg/kg to a maximum of 300 mg (0.13 to 0.33 mL/kg of a 3% solution, maximum 10 mL) by IV injection over 5 to 20 minutes, followed by sodium thiosulphate 400 mg/kg to a maximum of 12.5 g (as a 25 or 50% solution) by IV injection over 10 minutes.

Precautions:

» An increased clotting time has occurred l to 3 days after use of sodium thiosulphate.

» Sodium thiosulphate may exacerbate hypertension or oedema and should be used with caution in patients who may have these symptoms such as those with congestive heart failure, liver cirrhosis, renal impairment, and toxaemia of pregnancy.

Adverse Effects: The toxicity of sodium thiosulphate is low. Hypematraemia, hypotension, nausea and vomiting, diarrhoea, diuresis, and metabolic acidosis have been reported and are thought to be due to both the intrinsic osmotic properties of sodium thiosulphate, and from thiocyanate which is formed when sodium thiosulphate is used to treat cyanide poisoning. A salty taste in the mouth and a warm sensation over the body have also been reported.

Succimer (Dimercaptosuccinic Acid-DMSA)

ATC code: Not assigned

Capsule, 100 mg, LOU 5

Indications and dose

Adult

Lead and mercury poisoning: Give orally in a dose of 10 mg/kg or 350 mg/m2 every 8 hours for 5 days then every 12 hours for an additional 14 days. The course of treatment may be repeated if necessary, usually after an interval of not <2 weeks unless blood lead concentrations indicate the need for more prompt treatment.

Paediatric: Same as above.

Precautions: Mild to moderate neutropenia has been reported in some patients and regular full blood counts are recommended, treatment should be stopped or withheld

Pregnancy: Although data are scarce, there are reports of the use of succimer for poisoning in the second or third trimester of pregnancy, without adverse effects on the neonate

Hepatic and renal impairment: Use with caution. Liver functions should be measured at least once weekly during treatment.

Adverse Effects: GI disorders and increases in serum transaminases, flu -like symptoms, drowsiness, and dizziness have also occurred.

Note: For young children, succimer capsules can be opened and the succimer beads taken from a spoon or sprinkled on a small amount of soft food and swallowed.

6. Anticonvulsants/Antiepileptics

Acetazolamide

ATC code: S01EC01

Tablet, 250 mg, 500mg, LOU 5

Indications and dose

Adult

Adjunct in epilepsy and in refractory epilepsy, oral: 8-30mg/kg/day or daily dose divided to every 12 hours. Maximum dose 1g per day.

Paediatric

Child <12 years: Safety and efficacy not established

Child >12 years: *Adjunct in epilepsy and in refractory epilepsy, oral:* 8-30mg/kg/day or daily dose divided to every 6 to 12 hours; Not to exceed 30mg/kg/day or 1g per day.

For contraindications, Precautions, adverse effects, interactions and use in pregnancy and lactation, see section 22.4.

Carbamazepine

ATC code: N03AF01

Oral liquid, 100 mg/5 mL, LOU 4

Tablet (scored), 200 mg, LOU 4

Indications and dose

Adult

Generalized tonic–clonic and partial seizures, trigeminal neuralgia, generalized tonic–clonic seizures, partial seizures, oral: Initially 100–200 mg 1–2 times daily, increased gradually according to response to usual maintenance dose of 0.8–1.2 g daily in divided doses, in some cases, up to 1.6–2 g daily may be needed (in the **ELDERLY,** reduce the initial dose),

Trigeminal neuralgia, oral: Initially 100 mg 1–2 times daily, increased gradually according to response; usual dose, 200 mg 3–4 times daily (up to 1.6 g daily may be needed in some patients)

Note: Plasma concentration for optimum response, 4–12 mg/L (17–50 micromol/L)

Paediatric

Child 12–18 years: Initially 100–200 mg 1–2 times daily, increased gradually to usual maintenance dose of 400–600 mg 2–3 times daily

Child 1 month–12 years: Initially 5 mg/kg at night or 2.5 mg/kg twice daily, increased by 2.5–5 mg/kg every 3–7 days if necessary; usual maintenance dose of 5 mg/kg 2–3 times daily, in some cases, up to 20 mg/kg daily may be needed

Contraindications: Atrioventricular conduction abnormalities, history of bone marrow depression, porphyria.

Precautions: Hepatic impairment, renal impairment, cardiac disease, skin reactions, history of blood disorders (monitor blood counts before and during treatment), glaucoma, pregnancy and breastfeeding avoid sudden withdrawal.

Pregnancy: First trimester: Risk of teratogenesis including increased risk of neural tube defects (counselling and screening and adequate folate supplements advised, for example, 5 mg daily), risk of teratogenicity greater if more than one antiepileptic used, Third trimester: May possibly cause vitamin K deficiency and risk of neonatal bleeding, if vitamin K not given at birth, neonate should be monitored closely for signs of bleeding.

Breastfeeding: Continue breastfeeding, adverse effects possible, monitor infant for drowsiness.

Adverse effects: dizziness, drowsiness, headache, ataxia, blurred vision, diplopia (may be associated with high plasma levels), GI intolerance including nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhoea or constipation, commonly, mild transient generalized erythematous rash (withdraw if rash worsens or is accompanied by other symptoms), leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis, and aplastic anaemia), cholestatic jaundice, hepatitis, acute renal failure, SJS (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, and disturbances of bone metabolism with osteomalacia also reported, confusion and agitation in the elderly.

Interactions with other medicines: cyclosporine, clomipramine, oestrogens and progestogens, dexamethasone, doxycycline, erythromycin, ethosuximide, fluoxetine, furosemide, haloperidol, hydrochlorothiazide, hydrocortisone, protease inhibitors, isoniazid, levonorgestrel, levothyroxine, lithium, lopinavir, mebendazole, medroxyprogesterone, mefloquine, miconazole, nelfinavir, nifedipine, norethisterone, phenobarbital, praziquantel, prednisolone, spironolactone, valproic acid, vecuronium.

Notes:

- Blood, hepatic, or skin disorders: Patients or their Caregivers should be told how to recognize signs of blood, liver, or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develops. Leukopenia, which is severe, progressive, and associated with clinical symptoms requires withdrawal (if necessary, under cover of a suitable alternative antiepileptic
- Skilled tasks: May impair ability to perform skilled tasks, for example, operating
- machinery or driving.

Clobazam

ATC code: N05BA09

Tablet (scored), 10mg, LOU 4

Indications and dose

Adult:

Adjunct in treatment of seizures associated with Lennox Gastaut Syndrome (LGS), refractory status epilepticus and resistant adult focal epilepsy, oral: 20-30 mg/day in divided doses or once daily at bedtime and can be increased to a maximum of 60mg daily in divided doses.

Paediatric

As an adjunct in the treatment of seizures associated with Lennox Gastaut Syndrome (LGS) and refractory status epilepticus, oral:

Child 6-17 years ≤30kg: Initiate at 5mg daily and titrate as necessary at intervals of 7 days to a maximum of 20mg daily.

Child 6-17 years >30 kg: Initiate at 5mg twice a day and titrate as necessary and tolerated in intervals of 7 days up to 40mg daily.

Note: Unlicensed for use in children under 6 years, if required seek expert advice.

Contraindications: Respiratory depression, hypersensitivity to clobazam.

Precautions: Somnolence or sedation generally occurs during the first month of treatment and may diminish with continued treatment.

Renal and hepatic impairment: Responsiveness to clobazam and susceptibility to adverse effects is increased during hepatic and renal impairment. Dose adjustment is therefore necessary. Renal and hepatic functions should be monitored regularly.

Pregnancy: Not to be used in pregnancy and in women of childbearing potential. Limited available data shows evidence of occurrence of major malformations after exposure to benzodiazepines in the first trimester of pregnancy.

Breastfeeding: Not recommended in breastfeeding mothers since benzodiazepines are found in breastmilk.

Adverse effects: Decreased appetite, impaired consciousness, constipation, drug abuse, dry mouth, unsteady gait, loss of libido, nystagmus, skin reactions, speech impairment, suicidal behaviour, aggression, agitation, and increased weight.

Interactions with other medicines (*indicates serious): *Buprenorphine, *deflazacort, amitriptyline, aripiprazole, carbamazepine, cetirizine, etomidate, gabapentin, haloperidol, imipramine, isoniazid, and ketoconazole. Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.

Notes:

- Effectiveness may reduce significantly after weeks or months of continuous therapy.
- For epileptic patients maintain on a specific brand or generic clobazam product.
- Follow patients for signs and symptoms of respiratory depression and sedation.
- Daily doses of up to 30mg can be given as a single dose at bedtime. Higher doses should be divided.
- Clobazam can be confused with Clonazepam. Ensure the right drug is prescribed and dispensed.

Clonazepam

ATC code: N03AE01

Tablet, 0.5mg, 2 mg, LOU 4

Indications and dose

Adult

Adjunct treatment in all forms of epilepsy and various types of seizures such as absence seizures, myoclonic seizures, and recurrent acute repetitive seizures, oral: Initially 1mg once daily for four nights, dose to be increased every 3 days over 2-4 weeks until desired effect is achieved. Maintenance dose: 2-8mg daily adjusted according to response. May be taken once at night or in 3 or 4 divided doses.

Elderly: Initially 500 micrograms once daily for four nights, dose to be increased over 2-4 weeks. Maintenance dose: 2-8mg daily adjusted according to response. May be taken once at night or in 3 or 4 divided doses.

Paediatric:

Indicated as an adjunct treatment in all forms of epilepsy and various types of seizures such as absence seizures, myoclonic seizures, and recurrent acute repetitive seizures, oral:

Child 1–11 months: Initially 250 micrograms once daily for four nights, dose to be increased over 2–4 weeks, Usual dose: 0.5–1 mg daily at night but may be given in 3 divided doses, if necessary.

Child 1–4 years: Initially 250 micrograms once daily for four nights, dose to be increased over 2–4 weeks, usual dose 1–3 mg daily at night but may be given in 3 divided doses, if necessary.

Child 5–11 years: Initially 500 micrograms once daily for four nights, dose to be increased over 2–4 weeks, usual dose 3–6 mg daily at night but may be given in 3 divided doses, if necessary.

Child 12–17 years: Initially 1 mg once daily for four nights, dose to be increased over 2–4 weeks, usual dose 4–8 mg daily at night but may be given in 3–4 divided doses, if necessary.

Contraindications: Hypersensitivity to clonazepam or other benzodiazepines, acute narrow angle glaucoma, significant hepatic impairment, and respiratory insufficiency.

Precautions: May cause CNS depression and impair ability to handle hazardous tasks. Use with caution in patients with a history of abuse. Not recommended in patients with depressed neuroses, respiratory depression, and psychotic reactions. Abrupt withdrawal particularly in patients with long term

use may precipitate status epilepticus, gradual withdrawal is essential. Paradoxical reactions such as agitation, irritability, aggression, anger, nightmares, hallucinations, and psychoses may occur; they are more likely in children and the elderly, withdraw should this occur.

Hepatic impairment: Dose adjustments are necessary. Lower initial doses and extended dosing intervals are recommended. Patients with severe hepatic impairment should not be treated with clonazepam.

Renal impairment: No dose adjustments required.

Pregnancy: Not recommended in pregnancy since data for other benzodiazepines suggests possibility of adverse developmental effects.

Breastfeeding: Where possible, use alternative drugs. There are reports of sedation, poor feeding and poor weight gain in infants exposed to benzodiazepines through breastmilk. Infants exposed to this drug should be monitored for sedation, poor feeding and weight gain.

Adverse effects: Somnolence, abnormal coordination, ataxia, depression, dizziness, fatigue, memory impairment, restlessness, nervousness, anxiety, nightmares, vivid dreams, confusion, dysarthria, decreased libido, increased salivation, incomplete precocious puberty, headache, nystagmus, urticaria, pruritus, rash, transient hair loss and pigmentation changes.

Interactions with other medicines (*indicates serious): *Buprenorphine, *carbamazepine, *conivaptan, *olopatadine intranasal.

Notes:

- Risk of dependence and withdrawal increase with longer treatment duration.
- Stopping abruptly or reducing doses too quickly can result in withdrawal reactions.
- Suicidal thoughts and behaviour in patients on this drug have been reported.

Diazepam

ATC code: N05BA01

Rectal gel, 5 mg/mL, LOU 2

Indications and dose

Rectal gel is indicated for the management of selected refractory patients with epilepsy who are on stable regimens of anti-epileptic drugs who require diazepam intermittently to control bouts of increased seizure activity.

Adult

By rectum: 500 micrograms/kg, then 500 micrograms/kg after 12 hours as required

- **Elderly:** 250 micrograms/kg, then 250 micrograms/kg after 12 hours as required

Paediatric

By rectum

Neonate: 1.25–2.5 mg, then 1.25–2.5 mg after 10 minutes if required

Child 1 month–1 year: 5 mg, then 5 mg after 10 minutes if required

Child 2–11 years: 5–10 mg, then 5–10 mg after 10 minutes if required

Child 12–17 years: 10–20 mg, then 10–20 mg after 10 minutes if required

Contraindications: Chronic psychosis (in adults), CNS depression, compromised airway, hyperkinesis, respiratory depression

Precautions: Muscle weakness, organic brain changes, parenteral administration (close observation required until full recovery from sedation)

Renal impairment: Dose adjustments: Start with small doses in severe impairment.

Pregnancy: Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol.

Breastfeeding: Present in milk, and should be avoided if possible during breastfeeding.

Adverse Effects: Abnormal appetite, impaired concentration, movement disorders, muscle spasms, palpitations, sensory disorder, vomiting, constipation, diarrhoea, hypersalivation, speech slurred. Bradycardia, bronchial secretion increased', cardiac arrest, dry mouth, gynaecomastia, heart failure, leucopenia, loss of consciousness, memory loss, respiratory arrest, sexual dysfunction, syncope. Apnoea, nystagmus, anxiety. With rectal use: Skin reactions

Interactions with other medicines: Acetazolamide, amiloride, amlodipine, amitriptyline, atenolol, chlorpheniramine, chlorpromazine, clomipramine, codeine, enalapril, fluphenazine, furosemide, glyceryl trinitrate, haloperidol, halothane, hydralazine, hydrochlorothiazide, isoniazid, isosorbide dinitrate, ketamine, levodopa, methadone, methyldopa, morphine, nifedipine, nitrous oxide, phenytoin, promethazine, propranolol, rifampicin, ritonavir, sodium nitroprusside, spironolactone, thiopental, timolol, verapamil.

Gabapentin

ATC code: N03AX12

Tablet, 100 mg, 300 mg, LOU 4

Indications and dose

Adult

Adjunctive treatment of focal seizures with or without secondary generalization, oral: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day)

Peripheral neuropathic pain, oral: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially

300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response, maximum 3.6 g per day

Paediatric

Adjunctive treatment of focal seizures with or without secondary generalization, oral

Child 12–17 years: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response, usual dose 0.9–3.6 g daily in 3 divided doses (max. per dose 1.6 g 3 times a day); some children may not tolerate daily increments, longer intervals (up to weekly) may be more appropriate.

Child 6–11 years: 10 mg/kg once daily (max. per dose 300 mg) on day 1, then 10 mg/kg twice daily (max. per dose 300 mg) on day 2, then 10 mg/kg 3 times a day (max. per dose 300 mg) on day 3, usual dose 25–35 mg/kg daily in 3 divided doses, some children may not tolerate daily increments, longer intervals (up to weekly) may be more appropriate, daily dose maximum to be given in 3 divided doses, maximum 70 mg/kg per day.

Note: Not licensed at doses over 50 mg/kg daily in children under 12 years.

Contraindications: None listed

Precautions: Diabetes mellitus, elderly, high doses of oral solution in adolescents and adults with low body weight, history of psychotic illness, history of substance abuse, mixed seizures (including absences).

Renal impairment: Reduced doses of gabapentin are recommended for patients with renal impairment or those undergoing haemodialysis. Dose adjustments in adults:

- Reduce dose to 600–1800 mg daily in 3 divided doses if CrCl 50–79 mL/min.
- Reduce dose to 300–900 mg daily in 3 divided doses if CrCl 30–49 mL/min.
- Reduce dose to 150–600 mg daily in 3 divided doses if CrCl 15–29 mL/min (150 mg daily dose to be given as 300 mg in 3 divided doses on alternate days).
- Reduce dose to 150–300 mg daily in 3 divided doses if CrCl is less than 15 mL/min (150 mg daily dose to be given as 300 mg in 3 divided doses on alternate days).
- Dose adjustments in children: Reduce dose if EGFR is less than 80 mL/min/1.73 m2

Pregnancy:

Avoid unless benefit outweighs risk.

Breastfeeding:

Use only if potential benefit outweighs risk.

Adverse effects: Anxiety, abnormal appetite, arthralgia, asthenia, abnormal behaviour, confusion, constipation, cough, depression, diarrhoea, dizziness, drowsiness. dry mouth, dysarthria, dyspnoea, emotional lability, flatulence, gait abnormal, GI discomfort, headache, hypertension, increased risk of infection, insomnia, leucopenia, malaise, movement, disorders, muscle complaints, nausea, nystagmus, oedema, pain, abnormal reflexes, seizure (in children), abnormal sensation, sexual dysfunction, skin reactions, abnormal thinking, tooth disorder, tremor, vasodilation, vertigo, visual impairment, vomiting. Cognitive impairment, palpitations. Acute kidney injury, alopecia, angioedema, breast enlargement, drug use disorders, gynaecomastia, hallucination, hepatic disorders, hyponatraemia, pancreatitis, rhabdomyolysis, SCARs, thrombocytopenia, tinnitus, urinary incontinence.

Interactions with other medicines: Antacids containing aluminium with magnesium, Morphine

Notes:

- For those undergoing haemodialysis who have never received gabapentin, the recommended loading dose is 300 to 400 mg followed by 200 to 300 mg after each 4 hours of haemodialysis. On dialysis-free days no doses of gabapentin should be given.
- Capsules can be opened but the bitter taste is difficult to mask.
- Monitoring requirements: Monitor for signs of gabapentin abuse.

Lamotrigine

ATC code: N03AX09

Tablet (chewable/dispersible), 5 mg, 25 mg, LOU 4

Tablet, 25 mg, 100 mg, LOU 4

Indications and dose

Adult

Adjunctive therapy of seizures associated with Lennox-Gastaut syndrome with valproate, oral: Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then increased in steps of up to 50 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses; dose titration should be repeated if restarting after interval of more than 5 days.

Adjunctive therapy of focal seizures (with enzyme-inducing drugs) without valproate

Adjunctive therapy of primary and secondary generalised tonic-clonic seizures (with enzyme-inducing drugs) without valproate

Adjunctive therapy of seizures associated with Lennox-Gastaut syndromes (with enzyme-inducing drugs) without valproate, oral: Initially 50 mg once daily for 14 days, then 50 mg twice daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days, maintenance 200–400 mg daily in 2 divided doses, increased if necessary up to 700 mg daily, dose titration should be repeated if restarting after interval of more than 5 days.

Adjunctive therapy of seizures associated with Lennox-Gastaut syndromes (without enzyme-inducing drugs) without valproate, oral: Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided

doses; dose titration should be repeated if restarting after intervals of more than 5 days

Paediatric

Adjunctive therapy of seizures associated with Lennox-Gastaut syndrome with valproate, oral

Child 2–11 years (body weight up to 13 kg): Initially 2 mg once daily on alternate days for first 14 days, then 300 micrograms/kg once daily for further 14 days, then increased in steps of up to 300 micrograms/kg every 7–14 days; maintenance 1–5 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day.

Child 2–11 years (body weight 13 kg and above): Initially 150 micrograms/kg once daily for 14 days, then 300 micrograms/kg once daily for further 14 days, then increased in steps of up to 300 micrograms/kg ever 7–14 days; maintenance 1–5 mg/kg daily in 1–2 divided doses; dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day

Child 12–17 years: Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then increased in steps of up to 50 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses; dose titration should be repeated if restarting after interval of more than 5 days

Adjunctive therapy of focal seizures (with enzyme-inducing drugs) without valproate

Adjunctive therapy of primary and secondary generalised tonic-clonic seizures (with enzyme-inducing drugs) without valproate

Adjunctive therapy of seizures associated with Lennox-Gastaut syndromes (with enzyme-inducing drugs) without valproate, oral

Child 2–11 years: Initially 300 micrograms/kg twice daily for 14 days, then 600 micrograms/kg twice daily for further 14 days, then increased in steps of up to 1.2 mg/kg every 7–14 days; maintenance 5–15 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days, maximum 400 mg per day

Child 12–17 years: Initially 50 mg once daily for 14 days, then 50 mg twice daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 200–400 mg daily in 2 divided doses, increased if necessary up to 700 mg daily, dose titration should be repeated if restarting after interval of more than 5 days

Adjunctive therapy of seizures associated with Lennox-Gastaut syndromes (without enzyme inducing drugs) without valproate, oral

Child 2–11 years: Initially 300 micrograms/kg daily in 1–2 divided doses for 14 days, then 600 micrograms/kg daily in 1–2 divided doses for further 14 days, then increased in steps of up to 600 micrograms/kg every 7–14 days; maintenance 1–10 mg/kg daily in 1–2 divided doses; dose titration should be repeated if restarting after interval of more than 5 days, maximum 200 mg per day

Child 12–17 years: Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses; dose titration should be repeated if restarting after interval of more than 5 days.

Contraindications: Hypersensitivity

Precautions: Myoclonic seizures (may be exacerbated), Parkinson's disease (may be exacerbated)

Hepatic impairment: Caution is advised in moderate to severe impairment. Dose reduction of approximately 50% in moderate impairment, and approx. 75% in severe impairment, adjusted according to response.

Renal impairment: Caution in renal failure, metabolite may accumulate. Consider reducing maintenance dose in significant impairment.

Pregnancy: Plasma-drug concentration should be monitored before, during, and after pregnancy, including shortly after birth, and doses adjusted according to response - plasma levels alter during pregnancy and may increase rapidly after birth.

Breastfeeding: Present in milk, but limited data suggest no harmful effect on infant.

Adverse effects: aggression, agitation, arthralgia, diarrhoea, dizziness, drowsiness, dry mouth, fatigue, headache, irritability, nausea, pain, rash, sleep disorders, tremor, vomiting. Alopecia, movement disorders, vision disorders, Rare: confusion, conjunctivitis, disseminated intravascular coagulation, face oedema, fever, hallucination, hepatic disorders, lupus-like syndrome, lymphadenopathy, aseptic meningitis, multi organ failure, nystagmus, seizure, SCARs, including SJS and toxic epidermal necrolysis have developed (especially in children), Allergy and cross-sensitivity

Interactions: Antidepressant, antiepileptics, antimalarials, barbiturates, oral contraceptives, and paracetamol

Notes: Avoid abrupt withdrawal (taper off over 2 weeks or longer) unless serious skin reaction occurs.

Levetiracetam

ATC code: N03AX14

Injection (IV), 500 mg, LOU 5

Tablet (scored), 500 mg, LOU 4

Oral Solution, 100 mg/mL, LOU 5

Indications and dose

Adult

Monotherapy of focal seizures with or without secondary generalization, oral or by IV infusion: Initially 250 mg once daily for 1–2 weeks, then increased to 250 mg twice

daily, then increased in steps of 250 mg twice daily (max. per dose 1.5 g twice daily), adjusted according to response, dose to be increased every 2 weeks

Adjunctive therapy of focal seizures with or without secondary generalization, oral or by IV infusion: Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks.

Adjunctive therapy of myoclonic seizures and tonic-clonic seizures, oral or by IV infusion: Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks

Paediatric

Monotherapy of focal seizures with or without secondary generalization, oral or by IV infusion

Child 16–17 years: Initially 250 mg once daily for 1 week, then increased to 250 mg twice daily, then increased in steps of 250 mg twice daily (max. per dose 1.5 g twice daily), adjusted according to response, dose to be increased every 2 weeks

Adjunctive therapy of focal seizures with or without secondary generalization, oral:

Child 1–5 months: Initially 7 mg/kg once daily, then increased in steps of up to 7 mg/kg twice daily (max. per dose 21 mg/kg twice daily), dose to be increased every 2 weeks

Child 6 months–17 years (body weight up to 50 kg): Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks

Child 12–17 years (body weight 50 kg and above): Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 week

Adjunctive therapy of myoclonic seizures and tonic-clonic seizures, oral or IV infusion

Child 12–17 years (body weight up to 50 kg): Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks

Child 12–17 years (body weight 50 kg and above): Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2 weeks.

Contraindications: Hypersensitivity

Precautions: Somnolence and asthenia occur within four weeks of treatment – patients should be advised on signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience to know how levetiracetam affects them.

Hepatic impairment: Caution in severe impairment, maintenance dose reduction of 50% in severe impairment if CrCl is less than 60 mL/min/1.73 m2.

Renal impairment: Dose adjustments:

- In children: Reduce dose if estimated glomerular filtration rate less than 80 mL/min/1.73 m^2.
- In adults: Maximum 2 g daily if eGFR 50–80 mL/min/1.73 m^2, Maximum 1.5 g daily if eGFR 30–50 mL/min/1.73 m^2, Maximum 1 g daily if eGFR less than 30 mL/min/1.73 m^2

Pregnancy: The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. foetal growth should be monitored.

Breastfeeding: Present in milk, avoid use.

Adverse effects: Anxiety, decreased appetite, asthenia, abnormal behaviour, cough, depression, diarrhoea, dizziness, drowsiness, GI discomfort, headache, increased risk of infection, insomnia, mood altered, movement disorders, nausea, skin reactions, vertigo, vomiting, Alopecia, impaired concentration, confusion, hallucination, leukopenia, muscle weakness, myalgia, paraesthesia, psychotic disorder, suicidal tendencies, thrombocytopenia, vision disorders, weight changes, Acute kidney injury, agranulocytosis, hepatic disorders, hyponatraemia, neutropenia, pancreatitis, pancytopenia, personality disorder, rhabdomyolysis, SCARs, abnormal thinking.

Interactions: Methotrexate.

Notes:

- With IV use for IV infusion, dilute requisite dose with at least 100 mL glucose 5%or sodium chloride 0,9%, give over 15 minutes. With oral use for administration of oral solution, requisite dose may be diluted in a glass of water.
- If switching between oral therapy and IV therapy (for those temporarily unable to take oral medication), the IV dose should be the same as the established oral dose.

Lorazepam

ATC code: N05BA06

Injection, 4 mg/1-mL amp, LOU 2

Indications and dose

Adult

Convulsive status epilepticus, by slow IV injection: 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose, to be administered into a large vein

Paediatric

Convulsive status epilepticus, by slow IV injection

Child 1 month–11 years: 100 micrograms/kg (max. per dose 4 mg) for 1 dose, then 100 micrograms/kg after 10 minutes (max. per dose 4 mg) if required for 1 dose, to be administered into a large vein

Child 12–17 years: 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose, to be administered into a large vein

Note: In children, not licensed for use in febrile convulsions or convulsions caused by poisoning.

Contraindications: Avoid injections containing benzyl alcohol in neonates. CNS depression, compromised airway, respiratory depression.

Cautions: Muscle weakness, organic brain changes. A paradoxical increase in hostility and aggression may

be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects. Special precautions for parenteral administration: When given parenterally, facilities for managing respiratory depression with mechanical ventilation must be available. Close observation required until full recovery from sedation.

Renal impairment: Dose adjustments Start with small doses in severe impairment.

Breastfeeding: Benzodiazepines are present in milk, and should be avoided if possible, during breastfeeding.

Adverse effects: Common: Apnoea, asthenia, coma, disinhibition, extrapyramidal symptoms, hypothermia, memory loss, speech slurred, suicide attempt, Allergic dermatitis, constipation, sexual dysfunction, Rare: Agranulocytosis, hyponatraemia, pancytopenia, SIADH, Leucopenia, thrombocytopenia.

Interactions:

Rifampicin increases clearance of lorazepam.

Notes:

» For IV injection in children, dilute with an equal volume of sodium chloride 0.9% (for neonates, dilute injection solution to a concentration of 100 micrograms/mL). Give over 3–5 minutes, max. rate 50 micrograms/kg over 3 minutes. For IM injection in adults, solution for injection should be diluted with an equal volume of water for injections or sodium chloride 0.9%. For slow IV injection in adults, solution for injection should preferably be diluted with an equal volume of water for injections or sodium chlorideo.9%.

Magnesium Sulphate

ATC code: A12CC02

Injection, 500 mg/mL (50%) in 10-mL amp/vial, LOU 2

Indications and dose

Adult

Prevention of recurrent seizures in eclampsia by IV injection:

Initially 4 g over 5–15 minutes followed either by IV infusion 1 g/hour for at least 24 hours after the last seizure or delivery (whichever occurs later) or

by deep IM injection:

5 g into each buttock, then 5 g every 4 hours into alternate buttocks for at least 24 hours after the last seizure or delivery (whichever occurs later); recurrence of seizures may require an additional IV injection of 2 g (4 g if body weight over 70 kg).

Prevention of seizures in pre-eclampsia by IV infusion: Initially 4 g over 5–15 minutes followed either by IV infusion, 1 g/hour for 24 hours *or*

by deep IM injection:

5 g into each buttock, then 5 g every 4 hours into alternate buttocks for 24 hours; if seizure occurs, give an additional dose by IV injection of 2 g

Adolescent

Prevention of recurrent seizures in eclampsia, by IV injection:

Initially 4 g over 5–15 minutes followed either by IV infusion, 1 g/hour for at least 24 hours after the last seizure or delivery (whichever occurs later) or by deep IM injection, 5 g into each buttock, then 5 g every 4 hours into alternate buttocks for at least 24 hours after the last seizure or delivery (whichever occurs later); recurrence of seizures may require an additional IV injection of 2 g (4 g if body weight over 70 kg)

Prevention of seizures in pre-eclampsia by IV infusion

Initially 4 g over 5–15 minutes followed either by IV infusion, 1 g/hour for 24 hours or by deep IM injection, 5 g into each buttock, then 5 g every 4 hours into alternate buttocks for 24 hours; if seizure occurs, give an additional dose by IV injection of 2 g.

Contraindications: Hypersensitivity, myocardial damage, diabetic coma, heart block, hypermagnesemia, hypercalcemia, administration during the 2 hours preceding delivery in mothers with toxemia of pregnancy.

Precautions: myasthenia gravis, hepatic impairment, renal impairment.

Adverse effects: generally, those associated with hypermagnesaemia, including nausea, vomiting, thirst, flushing of skin, hypotension, arrhythmias, coma, respiratory depression, drowsiness, confusion, loss of tendon reflexes, and muscle weakness.

Interactions: Enhanced muscle relaxant effect with alcuronium, Profound hypotension reported with nifedipine and IV magnesium sulphate in pre-eclampsia, enhanced muscle relaxant effect with suxamethonium, Enhanced muscle relaxant effect with vecuronium.

Notes:

» **Dilution and administration:** For IV injection, the concentration of magnesium sulphate should not exceed 20% (dilute 1 part of magnesium sulphate injection, 50%, with at least 1.5 parts of water for injection), for IM injection, mix magnesium sulphate injection, 50%, with 1 mL lidocaine injection, 2%.

Midazolam

ATC code: N05CD08

Injection (as HCl), 1 mg/1 mL (5-mL amp), 5mg/mL (3-mL amp), LOU 4

Oral mucosal solution, 5 mg/1 mL, 10 mg/1mL, LOU 4

Indications and dose

Adult

Status epilepticus, by buccal administration: 10 mg, then 10 mg after 10 minutes, if required

Paediatric

Status epilepticus, febrile convulsions, by buccal administration:

Child 1–2 months: 300 micrograms/kg (max. per dose 2.5 mg), then 300 micrograms/kg after 10 minutes (max. per dose 2.5 mg), if required.

Child 3–11 months: 2.5 mg, then 2.5 mg after 10 minutes, if required.

Child 1–4 years: 5 mg, then 5 mg after 10 minutes, if required.

Child 5–9 years: 7.5 mg, then 7.5 mg after 10 minutes, if required.

Child 10–17 years: 10 mg, then 10 mg after 10 minutes, if required.

NOTE: Unlicensed Use: Oromucosal solution **NOT** licensed for use in **children under 3 months**. To be prescribed under specialist advise.

Initially by IV injection:

Neonate and child: Initially 150–200 micrograms/kg, followed by (*by continuous intravenous infusion*) 60 micrograms/kg/hour, (*by continuous intravenous infusion*) increased in steps of 60 micrograms/kg/hour every 15 minutes (max. per dose 300 micrograms/kg/hour) until seizure controlled.

NOTE: Unlicensed use: Injection **NOT** licensed for use in status epilepticus or febrile convulsions. To be prescribed under specialist advise.

Contraindications: CNS depression, compromised airway, severe respiratory depression, acute angle closure glaucoma, hypotension, and shock.

Precautions: Cardiac disease, children (particularly if cardiovascular impairment), concentration of midazolam in children under 15 kg not to exceed 1 mg/mL, debilitated patients (reduce dose). In children: hypothermia, hypovolaemia (risk of severe hypotension), In neonates: risk of airways obstruction and hypoventilation in children under 6 months (monitor respiratory rate and oxygen saturation), vasoconstriction. Recovery when used for sedation: Midazolam has a fast onset of action, recovery is faster than for other benzodiazepines such as diazepam, but may be significantly longer in the elderly, in patients with a low cardiac output, or after repeated dosing.

Hepatic impairment: For parenteral preparations caution is advised in all degrees of impairment. For parenteral preparations dose reduction in all degrees of impairment is recommended.

Renal impairment: Use with caution in chronic renal failure.

Breastfeeding: Small amount present in milk—avoid breastfeeding for 24 hours after administration (although amount probably too small to be harmful after single doses).

Adverse effects: Common: vomiting. Skin reactions. Rare: Dry mouth, dyspnoea, hiccups, movement disorders, respiratory disorders, Apnoea, bradycardia, cardiac arrest, constipation, physical assault, vasodilation, appetite increased, fall, saliva altered, thrombosis, disinhibition.

Interactions: Clarithromycin and erythromycin increase exposure to midazolam, lumacaftor reduces exposure to midazolam, Lorlatinib moderately decreases the exposure to midazolam

Notes:

» For IV infusion in adults give continuously in glucose 5% or sodium chloride 0.9%.

Oxcarbazepine

ATC code: N03AF02

Tablet, 150mg, 300mg, LOU 4

Indications and Dose

Adult

As an adjunct or alone for treatment of partial seizures with or without secondarily generalised tonic clonic seizures, oral:

Adjunctive treatment: 300 mg every 12 hours initially; may increase at weekly intervals by 600 mg/day up to 1200 mg/day

Monotherapy (if converting from other antiepileptic drug [AED]): Initially 300 mg every 12 hours; increased by 600 mg/day every week up to 2400 mg/day. Reduce and withdraw concomitant AED over 3-6 weeks while reaching maximum oxcarbazepine dose in 2-4 weeks

Monotherapy (if AED naive): Initially 300 mg every 12 hours; increased by 300 mg/day every 3 days to 1200 mg/day divided every 12 hours.

Paediatric:

Indicated for use as monotherapy or adjunctive therapy in children for the treatment of partial/focal seizures with or without secondary generalised tonic clonic seizures, oral:

Adjunctive treatment of partial seizures

Child 2-4 years and >20kg: Initially 8-10 mg/kg/day divided 12 hourly; not to exceed 600 mg/day.

Child 2-4 years and <20 kg: Consider starting with 16-20 mg/kg/day; may titrate to higher dose over 2-4 weeks; not to exceed 60 mg/kg/day.

Child 4-17 years: Initially 8-10 mg/kg/day divided 12 hourly; not to exceed 600 mg/day.

Target maintenance dose: May titrate to higher dose over 2 weeks to reach the following dosage ranges:

20 - 29 kg: 450 mg 12 hourly

29.1 - 39 kg: 600 mg 12 hourly

>39 kg: 900 mg 12 hourly

Monotherapy of partial seizures (if converting from another antiepileptic drug [AED]): Initially 8-10 mg/kg/day divided 12 hourly, while simultaneously reducing concomitant AEDs dose(s) over 3-6 weeks; may increase dose every week by maximum increment of 10 mg/kg/day.

Monotherapy (if AED naive): Initially 8-10 mg/kg/day divided 12 hourly; may increase every three days by 5 mg/kg/day to the following target maintenance doses:

20 – 24.99kg: 600-900 mg/day

25 - 34.99 kg: 900-1200 mg/day

35 - 44.99 kg: 900-1500 mg/day

45 – 49.99kg: 1200-1500 mg/day

50 - 59.99 kg: 1200-1800 mg/day

60 - 69.99 kg: 1200-2100 mg/day

70 kg: 1500-2100 mg/day

Contraindications: Known hypersensitivity to Oxcarbazepine or any of its components.

Precautions: Caution when performing tasks that require mental alertness, has been shown to cause an increased risk of suicidal thoughts and behaviour. Potentially fatal skin reactions may occur such as Steven Johnsons Syndrome

Hepatic impairment: No dose adjustment required in mild to moderate hepatic impairment. It has however not been evaluated in severe hepatic impairment and is therefore not recommended.

Renal impairment: If CrCl is <30ml/min decrease the usual starting dose by 50% and increase slowly to attain the desired clinical response.

Pregnancy: Data on oxcarbazepine on congenital malformations is limited however a structurally related carbamazepine is considered teratogenic. Risk cannot be excluded. Use should be carefully evaluated, considering aggravation of the illness is detrimental to both the mother and foetus. Consider minimum effective doses and monotherapy whenever possible.

Breastfeeding: Not to be used in lactating mothers since it is excreted in breastmilk and the effects on the infant are not well studied.

Adverse effects: Dizziness, diplopia, somnolence, nausea, nystagmus, vomiting, abdominal pain, ataxia, tremor, abnormal gait, fatigue, vertigo, vision abnormalities, asthenia, speech disorder, hypotension, muscle weakness, hyponatremia, speech disorder, rash, dyspepsia, agitation, and vertigo.

Interactions with other medicines (*indicates serious): Concomitant use is contraindicated with: Artemether Lumefantrine, Tenofovir emtricitabine, praziquantel, *Bedaquiline, *clopidogrel, *deflazacort, *dolutegravir, *ergotamine, *erythromycin, *ethinyl estradiol, *ivabradine, *ranolazine, *sildenafil, *sirolimus and *tolvaptan.

Notes:

- Women of childbearing potential should be advised to use highly effective contraception preferably non-hormonal such as intrauterine implants.
- Folic acid supplementation is recommended before and after pregnancy since it may cause folic acid deficiency.
- Avoid abrupt discontinuation due to increased seizure frequency and status epilepticus.

Phenobarbital

ATC code: N03AA02

Injection, 30 mg/1-mL amp LOU 2

Injection, 200 mg/1-mL amp, LOU 2

Tablet (scored), 30 mg, LOU 2

Indications and dose

Adult

Generalized tonic–clonic seizures, partial seizures, oral: 180 mg at night

Status epilepticus, by IV injection (dilute injection 1 in 10 with water for injection): 10 mg/kg at a rate of not more than 100 mg/min (up to a maximum total dose of 1 g)

Paediatric

Generalized tonic–clonic seizures, partial seizures, oral

Child: up to 8 mg/kg daily *Febrile convulsions, oral*

Child: Up to 8 mg/kg daily

Febrile convulsions, by IV injection (dilute injection 1 in 10 with water for injection)

Neonate: 5–10 mg/kg every 20–30 minutes up to plasma concentration of 40 mg/L

Status epilepticus by IV injection (dilute injection 1 in 10 with water for injection)

Child: 5–10 mg/kg at a rate of not more than 30 mg/min

Contraindications: porphyria, absence seizures.

Precautions: the elderly, debilitated, children (may cause behavioural changes), impaired renal function, impaired hepatic function respiratory depression (avoid if severe), pregnancy and breastfeeding, avoid sudden withdrawal, history of alcohol and drug abuse.

Adverse effects: sedation, mental depression, ataxia, nystagmus, allergic skin reactions including rarely, exfoliative dermatitis, toxic epidermal necrolysis, and SJS (erythema multiforme), paradoxical excitement, restlessness and confusion in the elderly, irritability and hyperactivity in children, megaloblastic anaemia (may be treated with folic acid), osteomalacia, status epilepticus (on treatment withdrawal), hypotension, shock, laryngospasm and apnoea (with IV injection).

Interactions: Plasma concentration of abacavir possibly reduced, Acetazolamide Increased risk of osteomalacia, Alcohol Enhanced sedative effect, Amitriptyline Antagonism of anticonvulsant effect (convulsive threshold lowered), metabolism of amitriptyline possibly accelerated (reduced plasma concentration), Amlodipine Probably reduced effect of amlodipine, Carbamazepine May be enhanced toxicity without corresponding increase in antiepileptic effect, plasma concentration of carbamazepine reduced, Chloramphenicol Metabolism of chloramphenicol accelerated (reduced plasma chloramphenicol concentration), Chlorpromazine Antagonism of anticonvulsant effect (convulsive threshold lowered), Ciclosporin Metabolism of ciclosporin accelerated (reduced effect), Clomipramine Antagonism of anticonvulsant effect (convulsive threshold lowered), metabolism of clomipramine possibly accelerated (reduced plasma concentration), Contraceptives, Oral Metabolism of estrogens and progestogens accelerated (reduced contraceptive effect),

Metabolism of dexamethasone accelerated (reduced effect), Metabolism of doxycycline accelerated (reduced plasma concentration), Ergocalciferol requirements possibly increased, Ethosuximide toxicity may be enhanced without corresponding increase in antiepileptic effect, plasma concentration of ethosuximide possibly reduced, Possibly reduced plasma concentration of etoposide, Fluoxetine Antagonism of anticonvulsive effect (convulsive threshold lowered), Fluphenazine Antagonism of anticonvulsant effect (convulsive threshold lowered), folinic acid Plasma concentration of phenobarbital possibly reduced, Griseofulvin Reduced absorption of griseofulvin (reduced effect), Haloperidol Antagonism of anticonvulsant effect (convulsive threshold lowered), metabolism of haloperidol accelerated (reduced plasma concentration), Hydrocortisone Metabolism of hydrocortisone accelerated (reduced effect), Plasma concentration of indinavir possibly reduced, Accelerated metabolism of levonorgestrel (reduced contraceptive effect), Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism), Plasma concentration of lopinavir possibly reduced, Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection), Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception), Metabolism of metronidazole accelerated (reduced plasma concentration), Plasma concentration of nelfinavir possibly reduced, Effect of nifedipine probably reduced, Accelerated metabolism of norethisterone (reduced contraceptive effect), Toxicity of phenytoin may be enhanced without corresponding increase in antiepileptic effect, Metabolism of prednisolone accelerated (reduced effect), Metabolism of quinidine accelerated (reduced plasma concentration), Plasma concentration of saquinavir possibly reduced, Toxicity of valproic acid may be enhanced without corresponding increase in antiepileptic effect, Effect of verapamil probably reduced, Metabolism of warfarin accelerated (reduced anticoagulant effect).

Notes:

- For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect. Plasma concentration for optimum response,15–40 mg/L (65–170 micromol/L).
- **Skilled tasks:** May impair ability to perform skilled tasks, for example operating machinery or driving.

Phenytoin Sodium

ATC code: N03AB02

Injection, 50 mg/1 mL (5-mL vial), LOU 4

Oral liquid, 30 mg/5 mL, LOU 4

Tablet/capsule, 50 mg, 100 mg, LOU 4

Indications and dose

Adult

Generalized tonic–clonic seizures, partial seizures, oral: Initially 3–4 mg/kg daily (as a single dose or in 2 divided doses), increased gradually at intervals of 2 weeks as necessary (with plasma phenytoin concentration monitoring) to a usual maintenance dose of 200–500 mg daily

Status epilepticus by slow IV injection or by IV infusion (with blood pressure and ECG monitoring): 15 mg/kg at a rate of not more than 50 mg/min, as a loading dose; maintenance doses of about 100 mg *oral* or *by slow IV injection* should be given thereafter at interval of 6–8 hours, with monitoring of plasma concentrations, rates and dose reduced according to weight

Paediatric

Generalized tonic–clonic seizures, partial seizures, oral

Child: Initially 3–5 mg/kg daily in 2 divided doses, increased gradually according to clinical response and plasma phenytoin concentration to a usual maintenance dose of 4–8 mg/kg daily (maximum, 300 mg daily)

Status epilepticus by slow IV injection or by IV infusion (with blood pressure and ECG monitoring)

Neonate: 5–20 mg/kg as a loading dose at rate of 1–3 mg/kg/min

Child: 15 mg/kg as a loading dose at rate of 1 mg/kg/min (not exceeding 50 mg/min)

Contraindications: porphyria, avoid parenteral use in sinus bradycardia, sinoatrial block, second- and third-degree heart block, Stokes-Adams syndrome.

Precautions: hepatic impairment (reduce dose), pregnancy (increased risk of birth defects and neonatal bleeding, and breastfeeding, diabetes mellitus, monitor blood counts, hypotension and heart failure (especially with parenteral use), in case of IV administration, resuscitation facilities must be available and the injection solution alkaline (irritant to tissues)

Adverse effects: gastric intolerance, headache, sleeplessness, agitation (during initial phase), sedation, confusion, blurred vision, ataxia, nystagmus, diplopia, slurred speech, cerebellar-vestibular symptoms, behavioural disorders, hallucinations, hyperglycaemia (may be signs of overdose), gingival hyperplasia, acne, coarse facies, hirsutism, fever, hepatitis, neurological changes including peripheral neuropathy, choreiform movements, impaired cognition, and increased seizure frequency, osteomalacia, rickets (associated with reduced plasma calcium levels), lymph-node enlargement, vertigo, rash (discontinue, if mild re-introduce cautiously, but discontinue if recurrence), very rarely SJS (erythema multiforme), SLE, and toxic epidermal necrolysis, rarely blood disorders including megaloblastic anaemia (may be treated with folic acid), leukopenia, thrombocytopenia, and agranulocytosis with or without bone marrow depression, with IV administration, cardiovascular and CNS depression (particularly if administered too rapidly) with arrhythmias, hypotension and cardiovascular collapse, and alterations in respiratory function (including respiratory collapse).

Interactions: Plasma concentration of abacavir possibly reduced, Increased risk of osteomalacia with acetazolamide, Acetylsalicylic acid enhances effect of phenytoin, Plasma phenytoin concentration reduced with regular large amounts of alcohol, Antagonism of muscle relaxant effect of alcuronium (accelerated recovery from neuromuscular blockade), Antagonism of anticonvulsant effect of amitriptyline (convulsive threshold lowered), possibly reduced plasma amitriptyline concentration, Probably reduced effect of amlodipine, Antacids (Aluminium

hydroxide, Magnesium hydroxide) reduce absorption of phenytoin, Azathioprine possibly reduce absorption of phenytoin, Bleomycin possibly reduce absorption of phenytoin, Carbamazepine may enhance toxicity of phenytoin without corresponding increase in antiepileptic effect, plasma concentration of phenytoin often lowered but may be raised, plasma concentration of carbamazepine often lowered, Chlorambucil possibly reduces absorption of phenytoin, Chloramphenicol increases plasma phenytoin concentration (increased risk of toxicity, Chloroquine possibly may increase risk of convulsions.

Notes:

- Patients or their caregivers should be told how to recognize signs of blood or skin disorders and advised to seek immediate medical attention if symptoms such as sore throat, rash, mouth ulcers, bruising, or bleeding develop leukopenia which is severe, progressive or associated with clinical symptoms requires withdrawal (if necessary, under cover of a suitable alternative antiepileptic).
- Phenytoin sodium may impair ability to perform skilled tasks, for example, operating machinery or driving.
- Plasma concentration for optimum response 10–20 mg/L (40–80 micromol/L). Preferably taken with or after food.

Pregabalin

ATC code N02BF02

Capsule, 25mg, 75mg, LOU 4

Adult:

Indications and dose:

As adjunctive therapy for treatment of partial onset seizures, oral: Initial dose of 150 mg/day every 8-12 hours. Maintenance dose is based on clinical response and tolerability, may increase dose in weekly increments; do not to exceed 600 mg/day.

Paediatric:

Indicated as adjunctive therapy for treatment of partial onset seizures in patients aged ≥1 month, oral:

Infant <1 month: Safety and efficacy not established.

Child ≥1 month to <17 years:

11 kg to <30 kg: Initially 3.5 mg/kg/day divided every 8 hours (for 1 month to 4 years) or every 4 to 12 hours (for ≥4 years). Maintenance dose: Based on clinical response and tolerability, may increase dose in weekly increments, not to exceed 14 mg/kg/day.

≥30 kg: Initially 2.5 mg/kg/day divided every 8 to 12 hours. Maintenance: Based on clinical response and tolerability, may increase dose in weekly increments up to 10 mg/kg/day (not to exceed 600 mg/day)

Child ≥17 years: Initially 150 mg/day divided every 8 to 12 hours. Maintenance: Based on clinical response and tolerability, may increase dose in weekly increments, not to exceed 600 mg/day

For contraindications, precautions, use in pregnancy and lactation, adverse events: **See section 3. 3.14**

Topiramate

ATC code: N03AX11

Tablet, 25mg, 50mg, LOU 5

Indications and dose

Adult

Monotherapy for the treatment of partial onset or primary generalized tonic clonic seizures, oral: 25mg 12 hourly and may increase by 50mg/day at weekly intervals to 200mg 12hourly.

Adjunctive therapy for the treatment of partial onset or primary generalized tonic clonic seizures, oral: Initially 25-50mg/day; increase by 25-50mg/day at weekly intervals to 100-200 mg every 12hours for partial onset seizures and 200mg every 12hours for primary generalized tonic clonic seizures.

Paediatric:

Monotherapy of generalised tonic-clonic seizures or focal seizures with or without secondary generalisation, oral:

Child <2 years: Safety and efficacy not established.

Child 2 to <10 years: 25 mg every night for 1 week. Titrate dose over 5-7 weeks to target daily maintenance dose (weight based) and divide into every 12hour dosing schedule.

Child 2 to <10 years weight-based maintenance dosing:

≤11 kg: 150 mg/day minimum; 250 mg/day maximum

12-22 kg: 200 mg/day minimum; 300 mg/day maximum

23-31 kg: 200 mg/day minimum; 350 mg/day maximum

32-38 kg: 250 mg/day minimum; 350 mg/day maximum

>38 kg: 250 mg/day minimum; 400 mg/day maximum

Child ≥10 years: Initially 25 mg every 12hours. Titrate by increments of 50 mg/week up to 200 mg every 12hours.

As adjunctive treatment of generalised tonic-clonic seizures or focal seizures with or without secondary generalisation, Adjunctive treatment for seizures associated with Lennox-Gastaut syndrome, oral:

Child <2 years: Safety and efficacy not established.

Child 2-16 years: Initially 25mg every night for the first week (based on 1-3mg/kg/day); increase dose by 1-3 mg/kg/day divided every 12hours at 1-2 weekly intervals up to 5-9 mg/kg/day divided 12 hourly.

Child ≥17 years: Initially 25-50 g/day; increase by 25-50mg/day at weekly intervals to 100-200 mg every 12 hours for partial onset seizures and 200 mg every 12hours for generalized tonic/clonic seizures.

Contraindications: Hypersensitivity to topiramate or its excipients.

Precautions: Formation of kidney stones associated with therapy. Increased fluid intake is necessary to increase urinary output. Use with caution in alcohol use. Withdraw gradually to reduce the risk of increased seizure frequency.

Hepatic impairment: Dose adjustments not necessary.

Renal impairment: Cr Cl <70 mL/min: Reduce dose by 50%. Cleared by hemodialysis at rate 4-6 times greater than normal; prolonged period of dialysis decrease topiramate serum concentrations.

Pregnancy: Not recommended in pregnancy due to an increased risk of congenital malformations.

Breastfeeding: Excreted in milk, effects of exposure in breastfed infants are unknown. Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need.

Adverse effects: Nervousness, ataxia, fatigue, dizziness, paresthesia, abnormal vision, anorexia, confusion, decreased serum bicarbonate, psychomotor slowing, nausea, speech disorder, alopecia, anaemia, anxiety, tremor, altered taste, vertigo, vomiting, skin reactions, eye disorders, urinary disorders, malaise, decrease in serum bicarbonate, dry mouth, asthenia,

Interactions with other medicines (*indicates serious): *Ergotamine, *erythromycin, *ethinyl estradiol, *ranolazine, *sirolimus, *tolvaptan, acetazolamide, alprazolam, amiodarone, amitryptiline, budesonide, buprenorphine, chlorpromazine, chlorzoxazne, clonazepam, clozapine,

Notes: Coadministration with valproic acid increases risk of hyperammonemia.

Valproic Acid

ATC code: N03AG01

Injection, 100 mg/1 mL (4-mL and 10mL amps), LOU 4

Oral liquid, 200 mg/5 mL, LOU 4

Tablet (e/c), 200 mg, 500mg, LOU 4

Tablet (crushable), 100 mg, LOU 4

Indications and dose

Adult

All forms of epilepsy, oral: Initially 600 mg daily in 2 divided doses, preferably after food, increased by 200 mg daily at 3-day intervals to a maximum of 2.5 g daily in divided doses, usual maintenance dose of 1–2 g daily (20–30 mg/kg daily).

Paediatric

All forms of epilepsy, oral

Child up to 20 kg: Initially 20 mg/kg daily in divided doses, may be increased provided plasma concentrations are monitored (above 40 mg/kg daily also monitor clinical chemistry and haematological parameters)

Child under 12 years: Over 20 kg, initially 400 mg daily in divided doses, increased until control (usually in range of 20–30 mg/kg daily), maximum, 35 mg/kg daily

Child over 12 years: Initially 600 mg daily in 2 divided doses, preferably after food, increased by 200 mg daily at 3-day intervals to a maximum of 2.5 g daily in divided doses, usual maintenance dose of 1–2 g daily (20–30 mg/kg daily). **Contraindications:** Active liver disease, family history of severe hepatic dysfunction, pancreatitis, porphyria.

Precautions: hepatic impairment (monitor liver function before and during first 6 months of therapy), especially in patients most at risk (including children under 3 years of age and those with metabolic disorders, degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation or multiple antiepileptic therapy, ensure no undue potential for bleeding before starting, and also before major surgery or anticoagulant therapy, renal impairment, pregnancy (increased risk of birth defects and neonatal bleeding), breastfeeding, SLE, false-positive urine tests for ketones, avoid sudden withdrawal.

Adverse effects: GI irritation, nausea, increased appetite, and weight gain, hyperammonemia, ataxia, tremor, transient hair loss (regrowth may be curly), oedema, thrombocytopenia, inhibition of platelet aggregation, impaired hepatic function and rarely fatal hepatic failure (withdraw treatment immediately if malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, drowsiness, or loss of seizure control, sedation reported and also increased alertness, behavioural disturbances, rarely pancreatitis (measure plasma amylase if acute abdominal pain), extrapyramidal symptoms, blood disorders (leukopenia, pancytopenia, red cell hypoplasia, and fibrinogen reduction), irregular periods, amenorrhoea, gynaecomastia, hearing loss, Fanconi syndrome, dementia, toxic epidermal necrolysis, SJS (erythema multiforme), vasculitis, hirsutism, and acne reported.

Interactions: Acetylsalicylic acid enhances of effect of valproic acid, Amitriptyline antagonises anticonvulsant effect (convulsive threshold lowered), Carbamazepine may be enhance toxicity without corresponding increase in antiepileptic effect, chloroquine Possibly increased risk of convulsions, Chlorpromazine antagonises anticonvulsant effect (convulsive threshold lowered), Clomipramine antagonises anticonvulsant effect (convulsive threshold lowered), Erythromycin possibly inhibits metabolism of valproic acid (increased plasma concentration), Ethosuximide may enhance toxicity without corresponding increase in antiepileptic effect, plasma concentration of ethosuximide possibly increased, Fluphenazine antagonism anticonvulsant effect (convulsive threshold lowered), Haloperidol antagonises anticonvulsant effect (convulsive threshold lowered), Mefloquine antagonises of anticonvulsant effect, Phenobarbital may enhance toxicity without corresponding increase in antiepileptic effect, plasma concentration of valproic acid reduced, plasma concentration of valproic acid reduced with phenobarbital, plasma concentration of phenytoin increased or possibly reduced, Warfarin Anticoagulant effect possibly enhanced Zidovudine Plasma concentration of zidovudine possibly increased (risk of toxicity).

Notes:

- Patients or their Caregivers should be told how to recognize signs of blood or liver disorders and advised to seek immediate medical attention if symptoms including loss of seizure control, malaise, weakness, anorexia, lethargy, oedema, vomiting, abdominal pain, drowsiness, jaundice, or spontaneous bruising or bleeding develop. Patients or their Caregivers should be told how to recognize signs of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea, and vomiting develop, discontinue if pancreatitis is diagnosed.
- Plasma concentrations in therapeutic range of 40–100 mg/L (280–700 micromol/L), not generally considered useful in assessing control, but higher levels associated with increased incidence of adverse effects, indicator of compliance, dose change or co-medication.

7. Anti-Infective Medicines

7.1. Anthelminthics

7.1.1. Intestinal Antihelminthics

Albendazole

ATC code: P02CA03

Tablet (chewable), 400 mg, LOU 1

Suspension, 100 mg/5 mL, LOU 1

Indications and dose

Adult

Hydatid disease (cystic echinococcosis, dog tapeworm), oral

Less than 60 kg: 15 mg/kg daily in 2 divided doses (maximum daily dose, 800 mg) for 28 days followed by 14 tablet-free days, up to 3 courses may be given

Over 60 kg: 800 mg daily in 2 divided doses for 28 days followed by 14 tablet-free days

Alveolar echinococcosis: Same as for cystic echinococcosis, but treatment cycles may need to be continued for months or years.

Neurocysticercosis (pork tapeworm, taenia solium), parenchymal disease

Over 60 kg: 800 mg daily in 2 divided doses for 8–30 days

Less than 60 kg: 15 mg/kg daily in 2 divided doses (maximum daily dose, 800 mg) for 8–30 days

Ascariasis, hookworm infections, enterobiasis, and trichostrongyloidiasis: 400 mg as a single dose (may be repeated in 3 weeks)

Whipworms (trichuriasis): 400 mg as a single dose (for moderate infections) or 400 mg daily for 3 days (severe infections)

Strongyloidiasis: 400 mg once or twice daily for 3–7 days; dose may be repeated after 3 weeks if necessary

Capillariasis: 400 mg daily for 10 days

Paediatric

Hydatid disease (cystic echinococcosis, dog tapeworm)

Child 2–17 years: 7.5 mg/kg twice daily (max. per dose 400 mg twice daily) for 28 days followed by 14-day break, repeated for up to 2–3 cycles

Ascariasis, hookworm infections, enterobiasis, and trichostrongyloidiasis

Child 12 months–2 years: 200 mg as a single dose (may be repeated in 3 weeks)

Child over 2 years: 400 mg as a single dose (may be repeated in 3 weeks)

Whipworms (trichuriasis)

Child 12 months–2 years: 200 mg as a single dose (for moderate infections)

or 200 mg initially then 100 mg twice daily for 3 days (severe infections).

Child over 2 years: 400 mg as a single dose (for moderate infections) or 400 mg daily for 3 days (severe infections).

Strongyloidiasis

Child over 2 years: 400 mg once or twice daily for 3–7 days; dose may be repeated after 3 weeks if necessary

Capillariasis

Child over 2 years: 400 mg daily for 10 days.

Contraindications: pregnancy (first trimester), hypersensitivity to benzimidazole compounds)

Precautions: liver function tests and blood counts recommended before longer-term treatment and twice during each cycle, exclude pregnancy before starting treatment (advise patients to use non-hormonal contraception during and for 1 month after treatment), breastfeeding, Special precautions in patients with neurocysticercosis, retinal lesions. May cause inflammatory reaction within the brain. Increased risk of bone marrow suppression in patient with liver disease.

Adverse effects: GI disturbances, headache, dizziness, increases in liver enzymes, reversible alopecia, rash, fever, Bone marrow suppression (leukopenia and rarely, pancytopenia), allergic shock if cyst leakage, convulsions and meningism in cerebral disease, blurred vision, rhabdomyolysis, acute renal failure, erythema multiforme, SJS.

Interactions: Plasma albendazole concentration possibly increased by dexamethasone, cimetidine, Increased plasma concentration of active metabolite of albendazole by praziquantel. Serum concentrations may decrease with carbamazepine, ritonavir, phenobarbital, and phenytoin.

Note: Administer with a high-fat meal

Mebendazole

ATC code: P02CA01

Tablet (chewable, dispersible), 500 mg, LOU 1

Indications and dose

Adult

Cystic echinococcosis, alveolar echinococcosis, oral: 4.5 g or 40–50 mg/kg/day in 3 divided doses for 6 months; in alveolar echinococcosis, treatment may be required for up to 2 years after radical surgery, or indefinitely in inoperable cases

Ascariasis, oral: 500 mg as a single dose or 100 mg twice daily for 3 days, may repeat in 3 weeks if necessary

Hookworm infections, trichuriasis, oral: 100 mg twice daily for 3 days; if eggs persist in the faeces, second course after 3–4 weeks; alternatively, (especially for mass treatment control programmes) *oral:* 500 mg as a single dose

Enterobiasis, oral: 100 mg as a single dose, repeated after intervals of 2–3 weeks, all household members over 2 years should be treated at the same time

Capillariasis, oral: 200 mg daily for 20–30 days

For mass treatment control programmes, oral: 500 mg as a single dose 4 times a year

Paediatric

Ascariasis, oral

Child over 2 years: 500 mg as a single dose or 100 mg twice daily for 3 days; may repeat in 3 weeks if necessary

Hookworm infections, trichuriasis, oral

Child over 2 years: 100 mg twice daily for 3 days; if eggs persist in the faeces, second course after 3–4 weeks; alternatively (especially for mass treatment control programmes), 500 mg as a single dose

Enterobiasis, oral

Child over 2 years: 100 mg as a single dose, repeated after intervals of 2–3 weeks; all household members over 2 years should be treated at the same time

Capillariasis, oral

Child over 2 years: 200 mg daily for 20–30 days; *For mass treatment control programmes,* 500 mg as a single dose 4 times a year

Contraindications: pregnancy, hypersensitivity

Precautions: blood counts and liver function tests recommended with high dose regimens, breastfeeding, children < 2 years

Adverse effects: GI disturbances, headache, dizziness, with high doses, allergic reactions, raised liver enzymes, alopecia, and bone marrow depression, exanthema, angioedema, urticaria, toxic epidermal necrolysis, SJS.

Interactions: Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection) with carbamazepine, phenobarbital, phenytoin. Increased plasma concentration with cimetidine. Co-administration of metronidazole may increase risk of SJS/toxic epidermal necrolysis.

Note: Doses should be taken between meals

Praziquantel

ATC code: P02BA01

Tablet, 600 mg, LOU 1

Indications and dose

Adult

Clonorchiasis/opisthorchiasi, oral: 25 mg/kg/dose 3 times daily for 1–2 days.

Taenia saginata and *T. solium* infections, *oral:* 5–10 mg/kg as a single dose.

Hymenolepis nana infection, *oral:* 15–25 mg/kg as a single dose.

Diphyllobothrium latum infection, *oral:* 5–10 mg/kg as a single dose.

Cysticercosis, oral: 50 mg/kg daily in 3 divided doses for 15 days with prednisolone (or similar corticosteroid) given 2–3 days before and throughout treatment period.

Dermal cysticercosis, oral: 60 mg/kg daily in 3 divided doses for 6 days.

Schistosomiasis, oral: 20 mg/kg 4–6 hourly for 3 doses or 40–60 mg/kg as a single dose

Paediatric

Clonorchiasis/opisthorchiasi, oral

Child over 4 years: 25 mg/kg/dose 3 times daily for 1–2 days.

Taenia saginata and *T. solium* infections, *oral*

Child over 4 years: 5–10 mg/kg as a single dose.

Hymenolepis nana infection, *oral*

Child over 4 years: 15–25 mg/kg as a single dose.

Diphyllobothrium latum infection, *oral*

Child over 4 years: 5–10 mg/kg as a single dose.

Cysticercosis, *oral*

Child over 4 years: 50 mg/kg daily in 3 divided doses for 15 days with prednisolone (or similar corticosteroid) given 2–3 days before and throughout treatment period.

Dermal cysticercosis, *oral*

Child over 4 years: 60 mg/kg daily in 3 divided doses for 6 days.

Schistosomiasis, *oral*

Child over 4 years: 20 mg/kg 4–6 hourly for 3 doses or 40–60 mg/kg as a single dose

Contraindications: Ocular cysticercosis, concomitant admin of strong CYP inducers (e.g., rifampicin).

Precautions: Neurocysticercosis (requires corticosteroid cover with monitoring in a hospital setting), patient with cardiac abnormalities, history of epilepsy and/or other signs of potential CNS involvement (e.g., SC nodules suggestive of cysticercosis), moderate to severe hepatic impairment.

Pregnancy and breastfeeding: avoid during, and for 72 hours, after treatment.

Adverse effects: abdominal discomfort, nausea, vomiting, diarrhoea, malaise, headache, dizziness, drowsiness, rarely hypersensitivity reactions including fever, urticaria, pruritus, and eosinophilia (may be due to dead and dying parasites), in neurocysticercosis, headache, hyperthermia, seizures, and intracranial hypertension (inflammatory response to dead and dying parasites in the CNS).

Interactions: Plasma praziquantel concentration reduced with CYP enzyme inducers, e.g., carbamazepine, dexamethasone, phenobarbital, phenytoin, chloroquine, Plasma praziquantel concentration increased by CYP enzyme inhibitors, e.g., cimetidine, erythromycin, itraconazole, ketoconazole. Concomitant use with rifampicin may cause subtherapeutic concentrations of praziquantel.

Notes:

» May impair ability to perform skilled tasks, for example operating machinery or driving.

7.1.2. Antifilarials

Management of lymphatic filariasis to be done with triple therapy regimen comprising albendazole + diethylcarbamazine dihydrogen citrate + ivermectin

Albendazole

ATC code: P02CA03

Tablet (chewable), 400 mg, LOU 1

Suspension, 100 mg/5 mL, LOU 1

Indications and dose

Adult

Filariasis, oral: 400mg as single dose in combination with ivermectin in areas where onchocerciasis is co-endemic; in areas where onchocerciasis is not co-endemic, 200mg as a single dose in combination with diethylcarbamazine.

Paediatric

Filariasis, oral:

Child > 2 years: As per adult dosing

Child < 2 years: 200mg as single dose in combination with ivermectin in areas where onchocerciasis is co-endemic; in areas where onchocerciasis is not co-endemic, 200mg as single dose in combination with diethylcarbamazine.

For Contraindications, Precautions, Adverse effects, Interactions and Notes: *See section 7.1.1 Intestinal Antihelminthics*

Diethylcarbamazine (Dec)

ATC code: P02CB02

Tablet (scored), 100 mg (as dihydrogen citrate), LOU 1

Indications and dose

Adult

Lymphatic filariasis due to Wuchereria bancrofti (bancroftian filariasis), Brugia malayi, or B. timori (it is also used in loiasis due to Loa loa and also for toxocariasis), oral: Initially, 1 mg/kg daily, increased gradually to 6 mg/kg daily over 3 days, preferably in divided doses after meals, for 21 days. A corticosteroid may be given concurrently; *for mass treatment program:* 6 mg/kg in divided doses over 24 hours, once a year.

Lymphatic filariasis (brugian), oral: 3–6 mg/kg, preferably in divided doses after meals, for 6–12 days; *for mass treatment control program:* 3–6 mg/kg in divided doses over 24 hours, 6 times at weekly or monthly intervals.

Occult filariasis, oral: 8 mg/kg daily for 14 days, repeated as necessary if symptoms return.

Loiasis, oral: 1 mg/kg as a single dose on the first day, doubled on two successive days, then adjusted to 2–3 mg/kg 3 times daily for a further 18 days.

Loiasis prophylaxis, oral: 300 mg weekly for as long as exposure occurs

Toxocariasis, oral: Initially, 1 mg/kg daily, increased gradually to 6 mg/kg daily over 3 days then maintained for 3 weeks.

Paediatric

Lymphatic filariasis (bancroftian), oral

Child under 10 years: half the dose of children over 10 years (below)

Child over 10 years: Initially, 1 mg/kg daily, increased gradually to 6 mg/kg daily over 3 days, preferably in divided doses after meals, for 21 days. A corticosteroid may be given concurrently.

For mass treatment program, oral

Child under 10 years: half the dose of children over 10 years (below)

Child over 10 years: 6 mg/kg in divided doses over 24 hours, once a year.

Lymphatic filariasis (brugian), oral

Child under 10 years: half the dose of children over 10 years (below)

Child over 10 years: 3–6 mg/kg, preferably in divided doses after meals, for 6–12 days

For mass treatment control program, oral

Child under 10 years: half the dose of children over 10 years (below)

Child over 10 years: 3–6 mg/kg in divided doses over 24 hours, 6 times at weekly or monthly intervals.

Toxocariasis, oral

Child over 10 years: Initially, 1 mg/kg daily, increased gradually to 6 mg/kg daily over 3 days then maintained for 3 weeks.

Contraindications: Pregnancy, hypersensitivity, breastfeeding, infants, elderly, or debilitated patients, impaired renal function, cardiac disease.

Precautions:

» Treatment with diethylcarbamazine should be closely supervised since hypersensitivity reactions are common and may be severe, especially in patients with onchocerciasis or loiasis.

» Avoid mass treatment schedules for infants, pregnant women, the elderly and debilitated patients, especially those with cardiac or renal disease.

» Caution if dizziness, loss of vision, night blindness, or tunnel vision occurs.

» Diethylcarbamazine should be administered with caution (e.g., gradually increasing doses) to prevent or minimize allergic reactions.

Adverse effects: itching of eyes and swelling of the face, fever, lymphadenopathy, skin rash and visual disturbances, nausea, vomiting, headache, dizziness, drowsiness. Mazzotti reaction characterized by rash, itching, headache, muscle and joint pains, tachycardia,

postural hypotension may start within 2 hours of drug administration. Encephalitis and retinal hemorrhage.

Notes:

» Diethylcarbamazine should be taken immediately after meals. Store in airtight containers at room temperature.

Ivermectin

ATC code: P02CF01

Tablet (scored), 3 mg, LOU 1

Indications and dose

Adult

Suppressive treatment of onchocerciasis, as a secondary agent in the treatment of bancroftian filariasis caused by Wucheria bancrofti (Bancroftian) filariasis. (Ivermectin is effective against the microfilariae of W. bancrofti but has no effect on the adult parasite.) Oral: 200 micrograms (0.2 mg) per kg of body weight as a single dose

Suppression of microfilariae, oral: 150 micrograms/kg as a single dose once a year

Onchocerciasis, oral: 150 micrograms/kg as single dose, repeat treatment every 3–12 months until symptoms resolved

Strongyloidiasis, oral: 200 micrograms/kg daily for 1–2 days

Paediatric

Suppression of microfilariae, oral

Child over 5 years (and weighing over 15 kg): 150 micrograms/kg as a single dose once a year

Onchocerciasis, oral

Children >15 kg: 150 micrograms/kg as single dose, repeat treatment every 3–12 months until symptoms resolved

Strongyloidiasis, oral

Child over 5 years: 200 micrograms/kg daily for1–2 days

Contraindications: pregnancy (delay treatment until after delivery), hypersensitivity to ivermectin.

Precautions: breastfeeding (avoid treating mother until infant is 1 week old).

Adverse effects: Mazotti like reaction, specifically arthralgia or myalgia (joint or muscle pain), dizziness, fever, headache, lymphadenopathy (painful and tender nodes in necks armpits, or groin), skin rash or itching - due to death of microfilariae in skin, or unusual tiredness or weakness, postural hypotension (lightheadedness while standing), increased serum alanine transferase (ALT), aspartate aminotransferase (AST), eosinophilia, decreased WBCs, increased haemoglobin, conjunctivitis, ocular hyperemia, irritation (topical), limbitis, punctate opacity, abnormal sensation, eyelid oedema, anterior uveitis, conjunctival hemorrhage Rarely, encephalopathy.

Interactions: Increased serum concentration with P-glycoprotein inhibitors. Decreased serum concentration with P-glycoprotein inducers. Enhanced anticoagulant effect of vitamin K antagonists, e.g., warfarin.

Notes:

» Avoid food or alcohol for at least 2 hours before and after a dose.

» Store at room temperature in a well-closed container.

7.2. Antibacterials

7.2.1. Access Group Antibiotics

Amikacin

ATC code: J01GB06

Injection, 50 mg (as sulphate)/1 mL in 2 mL vial, LOU 4

Injection, 250 mg (as sulphate)/1 mL in 2 mL vial, LOU 4

Indications and dos

Serious Gram-negative infections resistant to gentamicin (multiple daily dose regimen) by IM injection, or by slow IV injection, or by IV infusion: 15 mg/kg daily in 2 divided doses, increased to 22.5 mg/kg daily in 3 divided doses for up to 10 days, higher dose to be used in severe infections, maximum 1.5 g per day, maximum 15 g per course.

Serious Gram-negative infections resistant to gentamicin (once daily dose regimen) *by IV infusion over 30 – 60 minutes:* Initially 15 mg/kg once daily (max. per dose 1.5 g once daily), dose to be adjusted according to serum amikacin concentration, maximum 15 g per course.

Acute prostatitis (once daily dose regimen) by IV infusion, or by slow IV injection: Initially 15 mg/kg once daily (max. per dose 1.5 g once daily), dose to be adjusted according to serum amikacin concentration, maximum 15 g per cours

Acute pyelonephritis (once daily dose regimen)/Urinary tract infection (catheter-associated, once daily dose regimen), by IV infusion, or by slow IV injection: Initially 15 mg/kg once daily (max. per dose 1.5 g once daily), dose to be adjusted according to serum amikacin concentration, maximum 15 g per course.

To avoid excessive dosage in obese patients, use ideal weight for height to calculate dose and monitor serum amikacin concentration closely.

Paediatric

Serious Gram-negative infections resistant to gentamicin (multiple daily dose regimen)

By intramuscular injection, or by slow intravenous injection, or by Intravenous Infusion

Child 12–17 years: 7.5 mg/kg every 12 hours, increased to 7.5 mg/kg every 8 hours (max. per dose 500 mg every 8 hours) for up to 10 days, higher dose to be used in severe infection, to be administered over 3–5 minutes, maximum 15 g per course.

Child 1 month–11 years: 7.5 mg/kg every 12 hours, to be administered over 3–5 minutes.

Serious Gram-negative infections resistant to gentamicin (once daily dose regimen) *by IV infusion over 30 – 60 minutes*

Child: Initially 15 mg/kg once daily adjusted according to plasma-concentration monitoring, not to be used for endocarditis or meningitis, dose to be adjusted according to serum-amikacin concentration, intravenous injection to be administered over 3–5 minutes.

Acute pyelonephritis (once daily dose regimen)/ Urinary tract infection (catheter-associated, once daily dose regimen), by Intravenous Infusion, or by slow intravenous injection

Child 16–17 years: Initially 15 mg/kg once daily (max. per dose 1.5 g once daily), dose to be adjusted according to serum-amikacin concentration, maximum 15 g per course.

Child 3 months–15 years: Initially 15 mg/kg once daily, dose to be adjusted according to serum-amikacin concentration.

Neonatal sepsis (extended interval dose regimen), by slow IV injection, or by IV infusion

Neonate: 15 mg/kg every 24 hours, IV injection to be administered over 3–5 minutes

Neonatal sepsis (multiple daily dose regimen), by IM injection, or by slow IV injection, or by IV infusion

Neonate: Loading dose 10 mg/kg, then 7.5 mg/kg every 12 hours, IV injection to be administered over 3–5 minutes.

Pseudomonal lung infection in cystic fibrosis, by slow IV injection, or by IV infusion

Child: 10 mg/kg every 8 hours (max. per dose 500 mg every 8 hours), IV injection to be administered over 3–5 minutes.

Contraindications: Hypersensitivity to amikacin and other aminoglycoside antibiotics. Myasthenia gravis. Concomitant or sequential administration of oral or topical drugs that are neurotoxic, ototoxic or nephrotoxic, concomitant use with potent diuretics.

Precautions: Patient with pre-existing vertigo, tinnitus, or hearing loss, vestibular damage, neuromuscular disorders (e.g., Parkinson's disease), hypocalcaemia. Dehydrated patients, renal impairment, premature infants, neonates, children and elderly, pregnancy and breastfeeding.

Adverse effects:

Significant: **Hypersensitivity, neurotoxicity, ototoxicity, nephrotoxicity,** *Clostridium difficile*-associated diarrhoea (CDAD), pseudomembranous colitis (prolonged use), anaemia, eosinophilia, tinnitus, hypoacusis, vertigo, GI disturbances, pyrexia, injection site pain (IM), oliguria, azotaemia, RBC and/or WBC in urine, rash, pruritus, urticaria, fungal or bacterial superinfection.

Rare: Albuminuria, arthralgia, impaired balance, hypotension, muscle twitching, tremor. Apnoea (respiratory paralysis), neuromuscular blockade, paralysis.

Interactions: Increased risk of nephrotoxicity and ototoxicity with vancomycin, amphotericin B, bacitracin, cisplatin, ciclosporin, cephaloridine, paromomycin, polymyxin B, colistin, tacrolimus, viomycin, IV mannitol, capreomycin or other aminoglycosides, Enhanced effects of respiratory paralysis with anaesthetics or neuromuscular blocking agents (e.g., tubocurarine, succinylcholine, decamethonium, atracurium, rocuronium, vecuronium, opioid analgesic, massive transfusions with citrated anticoagulated blood), suxamethonium, Antagonism of effect of pyridostigmine and neostigmine, increased risk of ototoxicity with furosemide and ethacrynic acid., Incompatible with amphotericin chlorothiazide Na, erythromycin gluceptate, heparin, nitrofurantoin Na, phenytoin Na, thiopentone Na, warfarin Na, some penicillins and cephalosporins. May reduce antibacterial activity with penicillins.

Notes:

- With IV use multiple daily dose regimen: one-hour ('peak') serum concentration should not exceed 30 mg/L, pre-dose ('trough') concentration should be less than 10 mg/L. Once daily dose regimen: pre-dose ('trough') concentration should be less than 5 mg/L.
- For IV infusion, intermittent in glucose 5% or sodium chloride 0.9%. To be given over 30 minutes. Once daily dose regimen not to be used for endocarditis, febrile neutropenia, or meningitis. Consult local guidelines.

Amoxicillin

ATC code: J01CA04

Tablet (dispersible, scored), 250 mg, LOU 2

Capsule, 500 mg, LOU 2

Powder for oral liquid, 125 mg/5mL, 250 mg/5mL (as trihydrate), LOU 2

Indications and dose

Adult

Upper respiratory tract infections, bronchitis, otitis media, community acquired pneumonia, shigellosis

Infections due to sensitive organisms, oral: 500 mg every 8 hours or 750–1,000 mg every 12 hours, for severe infections 750–1,000 mg every 8 hours for 10 days

Severe or recurrent purulent respiratory-tract infections, oral: 3 g every 24 hours (750–1,000 mg every 8 hours)

Paediatric

Infections due to sensitive organisms, oral

Child up to 10 years: 125 mg every 8 hours, doubled in severe infections

Child over 10 years (≥ 40 kg): 500 mg every 8 hours or 750–1,000 mg every 12 hours, for severe infections 750–1,000 mg every 8 hours for 10 days.

Acute bacterial sinusitis, acute otitis media, cystitis, ear, nose, and/or throat infections, genitourinary infections, pyelonephritis, skin and soft tissue infections, oral

Child 3–10 years: 750 mg twice daily for 2 days

Contraindications: Known hypersensitivity (allergy) to any penicillins or other β-lactams (e.g., cephalosporins, carbapenems, monobactams), Infectious mononucleosis (suspected or confirmed).

Precautions: history of allergy, renal impairment and hepatic impairment, erythematous rashes common

in glandular fever, chronic lymphatic leukaemia, and possibly HIV infection, patients with reduced urine output, history of seizures, treated epilepsy or meningeal disorders, atopic individuals. Children. Pregnancy and breastfeeding.

Adverse effects: allergic reaction, specifically anaphylaxis (bronchospasm, sudden or severe decrease in blood pressure), anaphylactoid and SCARs (e.g., SJS, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms) skin rash, joint pain, fever, GIT reaction (mild diarrhoea, nausea, vomiting), oral candidiasis (sore mouth or tongue), pseudomembranous colitis (severe abdominal or stomach cramps and pain, abdominal tenderness, watery and severe diarrhoea), rarely, cholestatic hepatitis. tooth discolouration (brown, yellow, grey) particularly in children, vulvovaginal infection, elevated liver enzymes, changes in blood counts (prolonged therapy), convulsion (high doses), rarely, thrombocytopenia, leucopenia.

Interactions with other medicines: Decreased renal tubular secretion resulting in increased and prolonged serum concentration with probenecid. (except in cases of gonorrhea and other STD), Increased risk of allergic reactions (e.g., rashes) with allopurinol, tetracyclines, chloramphenicol, macrolides, and sulfonamides may interfere with the bactericidal effect of amoxicillin, may reduce the efficacy of oral contraceptives (e.g., estrogen/progesterone combination), may reduce the excretion and increase the toxicity of methotrexate methotrexate, may prolong prothrombin time (PT) or increase INR when used with oral anticoagulants, e.g., warfarin.

Notes:

» Store at room temperature in a tight container; oral suspension remains stable for 14 days at room temperature or if refrigerated.

Amoxicillin + Clavulanic Acid

ATC code: J01CR02

Tablet (dispersible, scored), Amoxicillin 250 mg + clavulanic acid 62.5 mg, LOU 4

Tablet, Amoxicillin 875 mg + clavulanic acid 125 mg, LOU 4

Powder for injection, Amoxicillin 500 mg + clavulanic acid 100 mg, LOU 4

Powder for injection, Amoxicillin 1000 mg + clavulanic acid 200 mg, LOU 4

Powder for oral liquid, Amoxicillin (as trihydrate) 200 mg + clavulanic acid (as potassium salt) 28 mg, LOU 4

Powder for oral liquid, Amoxicillin (as trihydrate) 125 mg + clavulanic acid (as potassium salt) 31.25 mg, LOU 4

Powder for oral liquid, Amoxicillin (as trihydrate) 250 mg + clavulanic acid (as potassium salt) 62.5 mg, LOU 4

Indications and dose

Adult

Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory-tract infections, exacerbations of chronic obstructive pulmonary disease, oral: 875 mg + 125 mg every 12 hours

Severe dental infection with spreading cellulitis, dental infection not responding to first-line antibacterial, oral: 250 mg + 62.5 mg every 8 hours for 5 days

Surgical prophylaxis, by IV injection, or by IV infusion: 1000 mg + 200 mg, to be administered up to 30 minutes before the procedure, then 1000 mg + 200 mg every 8 hours for up to 2–3 further doses in high-risk procedures. Administer normal IV or oral treatment course post-operatively, if clear signs of infection at operation is observed.

Community-acquired pneumonia, oral: 875 mg + 125 mg two or three times daily for 5 days

By IV injection, or by IV infusion: 1000 mg + 200 mg every 8 hours

Treatment infection by susceptible organisms, by IV infusion, or by IV injection: 1000 mg + 200 mg every 8 hours

Acute exacerbation of chronic obstructive pulmonary disease, oral: 875 mg + 125 mg twice a day for 5 days

By IV injection, or by IV infusion: 1000 mg + 200 mg every 8 hours

Bone and joint infections, osteomyelitis, oral:* 875 mg + 125 mg twice or three times a day (based on severity) for 14 days

***May require longer treatment periods**

Paediatric

Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory-tract infections, oral

Child 1–11 months: 125 mg + 31.25 mg three times a day (every 8 hours), dose doubled in severe infection.

Child 1–5 years: 250 mg + 62.5 mg three times a day (every 8 hours), dose doubled in severe infection.

Severe dental infection with spreading cellulitis, dental infection not responding to first-line antibacterial, oral

Child 1–11 months: 125 mg + 31.25 mg three times a day (every 8 hours), for 5 days, dose doubled in severe infection

Child 1–5 years: 250 mg + 62.5 mg three times a day (every 8 hours), for 5 days, dose doubled in severe infection.

Child 12–17 years: 250 mg + 62.5 mg three times a day (every 8 hours), for 5 days

Community-acquired pneumonia, oral

Child 1–11 months: 125 mg + 31.25 mg three times a day for 5 days, dose doubled in severe infection

Child 1–5 years: 250 mg + 62.5 mg three times a day for 5 days, dose doubled in severe infection.

Child 12–17 years: 250 mg + 62.5 mg every 8 hours (three times a day) for 5 days.

Acute exacerbation of bronchiectasis, oral

Child 1–11 months: 125 mg + 31.25 mg three times a day for 7 to 14 days

Child 1–5 years: 250 mg +62.5 mg three times a day for 7 to 14 days.

Child 12–17 years: 250 mg + 62.5 mg every 8 hours for 7 to 14 days

Acute sinusitis, oral

Child 1–11 months: 125 mg + 31.25 mg three times a day for 5 days.

Child 1–5 years: 250 mg +62.5 mg three times a day for 5 days.

Child 12–17 years: 250 + 62.5 mg every 8 hours for 5 days.

Acute otitis media, oral

Child 12–17 years: 250 mg + 62.5 mg three times a day for 5–7 days, alternatively 875 mg + 125 mg twice times a day for 5–7 days

Bone and joint infections, osteomyelitis, oral*

Child 1–11 months: 125 mg + 31.25 mg three times a day for 14 days, dose doubled in severe infection

Child 1–5 years: 250 mg + 62.5 mg three times a day for 14 days, dose doubled in severe infection.

Child 12–17 years: 250 mg + 62.5 mg every 8 hours for 14 days.

***May require longer treatment periods**

Contraindications: History of co-amoxiclav-associated jaundice or hepatic dysfunction, history of penicillin/β-lactam antibacterial-associated hypersensitivity, jaundice or hepatic dysfunction.

Precautions: Acute lymphocytic leukaemia (increased risk of erythematous rashes), chronic lymphocytic leukaemia (increased risk of erythematous rashes), cytomegalovirus (CMV) infection (increased risk of erythematous rashes), glandular fever (erythematous rashes common), maintain adequate hydration with high doses (particularly during parental therapy), accumulation of electrolytes contained in parenteral preparations can occur with high doses

Hepatic impairment: Manufacturer advises caution. Monitor liver function in liver disease.

Renal impairment: Risk of crystalluria with high doses (particularly during parenteral therapy). With intravenous use: Accumulation of electrolytes contained in parenteral preparations can occur in patients with renal failure.

Dose adjustments based on eGFR (for dosing adjustments in patients on haemodialysis, consult a specialist):

With oral use in adults:

Co-amoxiclav 875 mg + 125 mg tablets: In patients with creatinine clearance less than 30 ml/min, the use of Co-Amoxiclav presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

Co-amoxiclav 250 mg + 62.5 mg tablets: if eGFR 10–30 mL/minute/1.73m2, one 250 mg + 62.5 mg strength tablet every 12 hours; if eGFR less than 10 mL/minute/1.73m2, one 250 mg + 125 mg strength tablet every 24 hours.

With intravenous use in adults:

Co-amoxiclav injection: if eGFR 10–30 mL/minute/1.73m2, 1000 mg + 200 mg initially, then 500 mg + 100 mg every 12 hours; if eGFR less than 10 mL/minute/1.73m2, 1000 mg + 200 mg initially, then 500 mg + 100 mg every 24 hours.

With oral use in children:

Co-amoxiclav 125 mg + 31.25 mg suspension, or 250 mg + 62.5 mg suspension, or 200 mg + 28 mg dispersible tablets: use normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73m2. Use the normal dose recommended for mild or moderate infections every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73m2.

With intravenous use in children:

Co-amoxiclav injection: use normal initial dose and then use half normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73m2; use normal initial dose and then use half normal dose every 24 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73m2.

Pregnancy: Advised to avoid unless essential—may be associated with an increased risk of necrotising enterocolitis in neonates.

Breastfeeding: Trace amount in milk, but appropriate to use.

Adverse effects: Common: Increased risk of fungal or bacterial superinfection, dizziness, dyspepsia, headache. Rare: neutropenia. colitis haemorrhagic, crystalluria, hypersensitivity vasculitis, meningitis aseptic. With oral use: akathisia, black hairy tongue, cholangitis, Kounis syndrome. Potentially fatal: Severe hypersensitivity reactions, including anaphylactoid and SCARs (e.g., acute generalised exanthematous pustulosis), CDAD or pseudomembranous colitis. Rarely, hepatic dysfunction (e.g., cholestatic jaundice, hepatitis).

Interactions: Probenecid increases and prolongs plasma concentrations of amoxicillin, amoxicillin: Increased risk of allergic skin reactions with allopurinol, may reduce the efficacy of combined oral contraceptives, may reduce the excretion and increase the risk of methotrexate toxicity, may increase INR in patients maintained with oral anticoagulants, e.g., warfarin.

Ampicillin

ATC code: J01CA01

Powder for injection, 500 mg, LOU 4

Indications and dose

Adult

Use only to treat listeria, intrapartum prophylaxis, GI endoscopy (only recommended for high-risk patients undergoing high-risk procedures), listerial meningitis (in combination with another antibacterial), by *IV infusion:* 12 g daily in divided doses every 4–6 hours for 10–14 days

Chorioamnionitis/maternal sepsis of unknown source, IV injection: 2 g every 6 hours together with gentamycin

4 to 7 mg/kg (1 dose) and metronidazole 500 mg every 12 hours

Intrapartum prophylaxis, IV injection: 2 g intrapartum

GI endoscopy, IV injection: 2 g intrapartum 30 to 60 minutes before the procedure

Paediatric

Use only to treat listeria, intrapartum prophylaxis, GI endoscopy (only recommended for high-risk patients undergoing high-risk procedures, listerial meningitis (in combination with another antibacterial, by IV infusion

Neonate: Under 7 days, 50–100 mg/kg every 12 hours

Neonate: 7–21 days, 50–100 mg/kg every 8 hours

Neonate: 21–28 days, 50–100 mg/kg every 6 hours

Child: 1 month–12 years, 50 mg/kg every 4–6 hours (maximum, 2 g every 4 hours)

GI endoscopy, IV injection

Child: 50 mg/kg intravenously/intramuscularly (with or without gentamicin 1.5 mg/kg) within 30–60 minutes before procedure

Contraindications: hypersensitivity to penicillins.

Precautions: history of allergy, renal impairment, erythematous rash (common in glandular fever, acute or chronic lymphatic leukaemia, and CMV infection). Pregnancy and breastfeeding.

Adverse effects: nausea and vomiting, diarrhoea, rash (hypersensitivity or toxic response, may be indicative of a serious reaction — discontinue treatment), hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, and interstitial nephritis rarely antibiotic-associated colitis, neutropenia, thrombocytopenia, coagulation disorders. CNS toxicity (e.g., convulsions), paraesthesia, nephropathy, interstitial nephritis, hepatitis, cholestatic jaundice, moderate and transient increase in transaminases. Potentially Fatal: Anaphylaxis, CDAD

Interactions: Increased risk of rash with allopurinol, Effects of azathioprine enhanced and toxicity increased - reduce dose of azathioprine, Plasma ciclosporin concentration possibly increased (risk of nephrotoxicity), Possibly increased plasma concentration of didanosine, Increased risk of hypersensitivity, especially in renal impairment with hydrochlorothiazide, effects of mercaptopurine enhanced and toxicity increased - reduce dose of mercaptopurine, Anticoagulant effect of warfarin possibly enhanced. May reduce the efficacy of oral contraceptives. May reduce the efficacy of oral typhoid vaccines. May reduce the excretion of methotrexate. Reduced excretion with probenecid and sulfinpyrazone, resulting to increased risk of toxicity. Bacteriostatic antibacterials (e.g., erythromycin, chloramphenicol, tetracycline) may interfere with the bactericidal action of ampicillin.

Notes:

» Ampicillin use is restricted to Use in treatment of Listeria, for intra-partum prophylaxis, GI endoscopy (only recommended for high-risk patients undergoing high risk procedures)

Benzathine Benzylpenicillin

ATC code: J01CE08

Powder for injection, 900-mg (1.2 MU) vial, LOU 2

Indications and dose

Adult

Syphilis primary and secondary stage, by deep IM injection: 2.4 million units as a single dose; outer quadrant of the gluteus maximus or Hochstetter's ventrogluteal field is the preferred site of injection; if clinical symptoms recur or laboratory findings remain strongly positive, repeat treatment.

Syphilis (late-stage [latent seropositive]), by deep IM injection: 2.4 million units once weekly for 3 weeks; outer quadrant of the gluteus maximus or Hochstetter's ventrogluteal field is the preferred site of injection.

Paediatric

Congenital syphilis (where no evidence of CSF involvement) by deep IM injection

Child up to 2 years: 37.5 mg/kg as a single dose.

Contraindications: hypersensitivity to penicillins.

Precautions: history of allergy to cephalosporins, renal failure, heart failure, pregnancy and breastfeeding, history of allergy, asthma, seizure disorder. Not intended for IV or intra-arterial administration or injection near major peripheral nerves of blood vessels.

Adverse effects: hypersensitivity reactions including urticaria, fever, joint pains, rash, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, and interstitial nephritis, neutropenia, thrombocytopenia, coagulation disorders, rarely CNS toxicity (associated with high dosage or severe renal failure), Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins), rarely nonallergic (embolic–toxic) reactions, pain and inflammation at injection site, hypotension, tachycardia, palpitations, pulmonary HTN, pulmonary embolism, vasodilation, vasovagal reaction, cerebrovascular accident, syncope.

Interactions: Oral contraceptive effect of estrogens possibly reduced (risk probably small), Reduced excretion of methotrexate (increased risk of toxicity). Potentially fatal: Anaphylaxis, antibiotic-associated pseudomembranous colitis.

Benzylpenicillin (Penicillin G)

ATC code: J01CE10

Powder for injection, 600 mg (1 MU) (as a sodium or potassium salt) vial, LOU 2

Powder for injection, 3 g (5 MU) (as a sodium or potassium salt) vial, LOU 4

Indications and dose

Adult

Mild to moderate infections due to sensitive organisms, by IM injection, by slow IV injection or by IV infusion: 2.4–4.8 g daily in 4 divided doses, with higher doses in severe infections.

Bacterial endocarditis, by slow IV injection or by IV infusion: 7.2–14.4 g daily in 6 divided doses

Meningococcal disease, by slow IV injection or by IV infusion: 2.4 g every 4 hourly. Max: 18 g/day in meningococcal meningitis

Suspected meningococcal disease (before referral to hospital), by IM injection or by slow IV injection: 1.2 g

Neurosyphilis, by slow IV injection: 1.8–2.4 g every 4 hours for 2 weeks

Paediatric

Mild to moderate infections due to sensitive organisms, by IM injection, by slow IV injection or by IV infusion

Neonate under 1 week: 50 mg/kg daily in 2 divided doses

Neonate 1–4 weeks: 75 mg/kg daily in 3 divided doses.

Child 1 month–12 years: 100 mg/kg daily in 4 divided doses, with higher doses in severe infections.

Meningococcal disease, by slow IV injection or by IV infusion

Premature infant and neonate under 1 week: 100 mg/kg daily in 2 divided doses.

Neonate 1–4 weeks: 150 mg/kg daily in 3 divided doses.

Child 1 month–12 years: 180–300 mg/kg daily in 4–6 divided doses.

Suspected meningococcal disease (before referral to hospital), by IM injection or by slow IV injection

Infant under 1 year: 300 mg

Child 1–9 years: 600 mg

Child over 10 years: 1.2 g

Congenital syphilis, by slow IV injection, by IM injection or slow IV injection

Child up to 2 years: 30 mg/kg twice daily for the first 7 days of life, then 30 mg/kg 3 times daily for 3 days

Child over 2 years: 120–180 mg/kg (maximum, 1.44 g) daily in 4–6 divided doses for 10–14 days

Contraindications: hypersensitivity to penicillins, avoid intrathecal route.

Precautions: history of allergy to β-lactam allergy and/or asthma, seizure disorder, renal failure, heart failure, pregnancy and breastfeeding, diabetic patients.

Adverse effects: hypersensitivity reactions including urticaria, fever, joint pains, rash, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, and interstitial nephritis, diarrhoea, antibiotic-associated colitis, neutropenia, thrombocytopenia, coagulation disorders, CNS toxicity including convulsions, coma, and encephalopathy (associated with high dosage or severe renal failure), electrolyte disturbances, Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins), inflammation, phlebitis or thrombophlebitis at injection sites. Potentially fatal: Anaphylaxis, pseudomembranous colitis.

Interactions: Oral contraceptive effect of estrogens possibly reduced (risk probably small), Reduced excretion of methotrexate (increased risk of toxicity). Increased plasma concentration with probenecid. Antagonism of bactericidal effect with bacteriostatic antibacterials (e.g., erythromycin, tetracyclines).

Notes:

IV route preferred for neonates and infants, doses over 1.2 g should be given by the IV route only.

Cefalexin

ATC code: J01DB01

PFOL, 125mg/5mL, LOU 2

Capsule , 250 mg, LOU 2

Indications and dose

Adult

Skin and soft tissue infections, streptococcal pharyngitis and mild uncomplicated urinary tract infections: 250mg every 6 hours or 500mg every 12 hours

Hospital Acquired Pneumonia: 500mg two to three times a day, up to 1.5g three to four times a day

Prophylaxis of recurrent UTI (urinary tract infections): 125mg once daily alternatively 500mg once following a trigger

Catheter associated UTI: 500mg two to three times for 7 to 10 days (increased up to 1.5g grams three to four times a day in severe infections)

Note:

- Severe otitis media; 75-100mg/kg/day in four divided doses
- Purulent Otitis media and skin and soft tissue infections a therapeutic dose should Be administered for 10 days

Paediatric

Skin and soft tissue infections, streptococcal pharyngitis and mild uncomplicated urinary tract infections

Neonate: 25-50mg/kg in two divided doses

Infant or **child <2 years:** 25-50mg/kg in two divided doses, alternatively 125mg twice daily

Child 5–11 years: 12.5mg/kg, alternatively 250mg three times a day

Child 12–17 years: 500mg two to three times a day

Prophylaxis of recurrent UTI

Paediatric; 12.5mg/kg once daily (maximum 125 mg)

Child 16–17 years; 125mg once daily, alternatively 500mg for one dose following exposure to a trigger

Catheter associated UTI

Child 1–11 months; 12.5mg/kg twice daily 7-10 days alternatively 125mg twice daily. In severe infections 25mg/kg two to four times a day (up to 1g four times a daily)

Child 1–4 years; 12.5mg/kg twice daily, alternatively 125mg three times daily for 7-10 days. Severe infections 25mg/kg two to four times daily (up to 1g four times a day)

Child 5–11 years; 12.5 mg/kg twice daily alternatively 250mg thrice daily for seven to ten days. Severe infections 25mg/kg two to four times daily (maximum 1g four times daily)

Child 12–17 years; 500mg two to three times a day for seven to ten days. Severe infections up to 1.5g three to four times a day.

Contraindications: Contraindicated in patients with hypersensitivity to cephalosporins

Precautions: History of hypersensitivity reactions to penicillins and cephalosporins. Positive direct coombs test has been reported during treatment with cephalosporin antibiotics.

Renal impairment: Dose adjustments:

In adults Maximum 3 g daily if eGFR 40–50 mL/minute/1.73 m2

Maximum 1.5 g daily if eGFR 10–40 mL/minute/1.73 m2

Maximum 750 mg daily if eGFR less than 10 mL/minute/1.73 m2

In children Reduce dose in moderate impairment

Pregnancy: No evidence of teratogenicity however, caution should be exercised when prescribing for the pregnant patient

Breastfeeding: Caution should be exercised when administered to a nursing woman since it is present in milk in low concentrations

Adverse effects: Nausea, vomiting, diarrhea, dyspepsia, transient hepatitis, cholestatic jaundice, rash, urticaria, angioedema, rarely erythema multiforme, Steven Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, eosinophilia, neutropenia, thrombocytopenia, hemolytic anemia, genital and anal pruritis, candidiasis, vaginitis, vaginal discharge, agitation, confusion, fatigue, headache, hallucination, arthralgia, arthritis, slight elevation in AST (Aspartate transaminase) and ALT (Alanine transaminase)

Interactions with other medicines: Administration with other nephrotoxic drug substances such as aminoglycosides, other cephalosporins, and furosemide and similar potent diuretics may increase the risk of nephrotoxicity. Renal excretion of cephalexin is inhibited by probenecid. Cephalexin increases the plasma metformin concentration. Hypokalemia has been observed in patient taking cephalexin with cytotoxic drugs and gentamicin.

Cefazolin

ATC code: J01DB04

Powder for injection, 500 mg, 1 g (as a sodium salt) in a vial, LOU 4

Indications and dose

Adult

Prophylaxis of infection in surgery, by deep IM injection, by IV injection (over at least 3–5 minutes), or by IV infusion: 1 g as a single dose at induction of anaesthesia, or after cord clamping in caesarean section, followed by 0.5–1 g during surgery for lengthy procedures (repeated if necessary if surgery lasts over 3 hours) then 0.5–1 g every 6–8 hours after surgery for 24 hours.

Respiratory tract, skin and skin structure, genital, urinary tract, biliary tract, bone and joint infections, septicemia, by deep IM injection, by IV injection (over at least 3–5 minutes), or *by IV infusion:* 250 mg to 2 g every 6–12 (usually 8) hours, depending on severity of infection, maximum dose: 12 g/day.

Paediatric

Prophylaxis of infection in surgery, by deep IM injection, by IV injection (over at least 3–5 minutes), or by IV infusion

Child: 25 mg/kg (maximum, 1 g) as a single dose at induction of anaesthesia, repeated if necessary if surgery lasts over 3 hours; further doses may be given every 6–8 hours postoperatively for 24 hours if necessary.

Respiratory tract, skin and skin structure, genital, urinary tract, biliary tract, bone and joint infections, septicemia, by deep IM injection, by IV injection (over at least 3–5 minutes), or *by IV infusion*

Child older than 1 month: 25–100 mg/kg/day divided every 6–8 hours, maximum: 6 g/day

Contraindications: hypersensitivity to cefalosporins.

Precautions: sensitivity to beta lactam antibacterials (avoid if history of immediate hypersensitivity reactions, moderate renal impairment, pregnancy and breastfeeding, use may result in false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test.

Adverse effects: Diarrhoea, nausea, rash, electrolyte disturbances, cholestatic hepatitis, pain and inflammation at injection site, antibiotic-associated colitis, less commonly vomiting, headache, dizziness, and fever, rarely confusion (particularly following large doses and in renal impairment), arthritis, serum sickness-like reactions, neurotoxicity (including seizures), blood disorders (including neutropenia, eosinophilia, thrombocytopenia, leucopenia, thrombocythemia, haemolytic anaemia, and bleeding), renal impairment (including interstitial nephritis), allergic reactions (including urticaria, anaphylaxis, angioedema, and bronchial obstruction), and abnormal liver function tests, erythema multiforme and toxic epidermal necrolysis also reported.

Interactions: Possibly enhances the anticoagulant effect of warfarin. Probenecid may decrease renal tubular secretion of cefazolin, resulting in increased and prolonged blood levels. May increase the nephrotoxic effects of aminoglycosides. May decrease the protein binding of fosphenytoin and phenytoin. Disulfiram-like reaction with alcohol.

Notes:

IM administration may be painful and should be avoided where possible.

Doxycycline

ATC code: J01AA02

Capsule, 100 mg (HCl), LOU 2

Indications and dose

Susceptible Bacterial infections, oral using i/r,

Adult

Acne, oral: 40 mg or 50 mg (depending on the preparation) daily for 6–12 weeks

Syphillis, oral: 300 mg daily in divided doses for at least 10 days

Uncomplicated genital chlamydia, non-gonococcal urethritis, oral: 100 mg 12 hourly for 7 days

Lyme disease (erythema migrans and/or non-focal symptoms, affecting cranial nerves or peripheral nervous system), Lyme carditis, oral: 100 mg 12 hourly for 10 – 14 days (may be continued for 21 days in neurological and cardiac disease)

In refractory urinary-tract infections and sexually transmitted diseases, oral: 200 mg daily

Cellulitis, erysipelas, oral: Initially 200 mg daily for 1 dose, then maintenance 100 mg once daily for 5–7 days in total then review. Severe infections: 200 mg daily

Paediatric

Susceptible infections (e.g., chlamydia, rickettsia and mycoplasma), oral

Child 8–11 years (administered on expert advice) (bodyweight up to 45 kg): Initially 4.4 mg/kg daily in 1–2 divided doses for 1 day, then maintenance 2.2 mg/kg daily in 1–2 divided doses

Child 8–11 years (administered on expert advice) (bodyweight 45 kg and above): Initially 200 mg daily in 1–2 divided doses for 1 day, then maintenance 100 mg daily

Child 12–17 years: Initially 200 mg daily in 1–2 divided doses for 1 day, then maintenance 100 mg daily

Severe infections (including refractory urinary-tract infections), oral

Child 8–11 years (administered on expert advice) (bodyweight up to 45 kg): Initially 4.4 mg/kg daily in 1–2 divided doses for 1 day, then maintenance 2.2–4.4 mg/kg daily in 1–2 divided doses

Child 12–17 years: 200 mg daily

Acute sinusitis, acute cough [if systemically very unwell or at higher risk of complications], community-acquired pneumonia, oral

Child 12–17 years: Initially 200 mg daily for 1 dose, then maintenance 100 mg once daily for 5 days in total.

Acute exacerbation of bronchiectasis, oral

Child 12–17 years: Initially 200 mg daily for 1 dose, then maintenance 100 mg once daily for 7–14 days in total

Acne, oral

Child 12–17 years: 100 mg once daily

Early syphilis, oral

Child 12–17 years: 100 mg twice daily for 14 days

Late latent syphilis, oral

Child 12–17 years: 100 mg twice daily for 28 days

Uncomplicated genital chlamydia, non-gonococcal urethritis, oral

Child 12–17 years: 100 mg twice daily for 7 days

Pelvic inflammatory disease, oral

Child 12–17 years: 100 mg twice daily for 14 days

Lyme disease [erythema migrans and/or non-focal symptoms, affecting cranial nerves or peripheral nervous system], Lyme carditis, oral

Child 9–11 years (administered on expert advice) (bodyweight up to 45 kg): Initially 5 mg/kg in 2 divided doses on day 1, then 2.5 mg/kg daily in 1–2 divided doses for a total of 21 days, increased if necessary up to 5 mg/kg daily for 21 days, increased dose used in severe infections, maximum 200 mg per day

Child 9–11 years (administered on expert advice) (bodyweight 45 kg and above): 200 mg daily in 1–2 divided doses for 21 days

Child 12–17 years (administered on expert advice): 200 mg daily in 1–2 divided doses for 21 days

In refractory urinary-tract infections and sexually transmitted diseases, oral

Child 12–17 years: 200 mg daily

Cellulitis, erysipelas, oral

Child over 8 years: 2 mg/kg (maximum 100 mg) twice daily on day 1, then 2 mg/kg (maximum 100 mg) daily, or twice daily in severe infections such as rickettsia; maximum daily dose 200 mg.

Contraindications: Pregnancy, breastfeeding, porphyria, SLE, hypersensitivity to doxycycline and other tetracycline congeners, pregnancy, and breastfeeding, Concomitant use of methoxyflurane.

Precautions: Children under 8 years (avoid unless life-threatening infection when no other alternative exists), avoid exposure to sunlight or sunlamps (photosensitivity reported), renal impairment, hepatic impairment, concomitant hepatotoxic drugs, myasthenia gravis.

Hepatic impairment: Avoid (or use with caution).

Renal impairment: Use with caution, avoid excessive doses.

Adverse effects: Common: GI intolerance (nausea, vomiting, diarrhoea, epigastric burning), tooth discoloration (permanent in children aged < 8 years), enamel dysplasia, reduced bone growth (in children < 8 years), photosensitivity (depends on dose and degree of sun exposure). Rash, stomatitis, bone deformity, fungal overgrowth.

Rare: Photo-onycholysis and nail discoloration, oesophageal ulcers (due to partly swallowed tablets or capsules), antibiotic-associated colitis (CDAD), hepatitis, fatty liver degeneration (with high doses, especially in pregnancy), pancreatitis, hepatotoxicity, headache and visual disturbances may indicate benign intracranial hypertension, bulging fontanelles in infants, allergic reactions including anaphylaxis (less common than with penicillins), toxic epidermal necrolysis, worsening of SLE, serum sickness-like reactions, Jarisch- Herxheimer reaction when treating spirochetal infections.

Interactions (*indicates serious):

- Antacids (aluminium hydroxide, magnesium hydroxide): reduced absorption of doxycycline.
- Carbamazepine: accelerated metabolism of doxycycline (reduced effect).
- *Ciclosporin: possibly increased plasma ciclosporin concentration.
- Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).
- Ferrous salts: absorption of oral ferrous salts reduced by doxycycline, absorption of doxycycline reduced by oral ferrous salts.
- Methotrexate: increased risk of methotrexate toxicity.
- Phenobarbital: metabolism of doxycycline accelerated (reduced plasma concentration).
- Phenytoin: increased metabolism of doxycycline (reduced plasma concentration).
- Rifampicin: plasma doxycycline concentration possibly reduced.
- *Warfarin: anticoagulant effect possibly enhanced.
- Tetracyclines may interfere with the bactericidal action of penicillin.
- Risk of pseudotumour cerebri with isotretinoin.

Notes:

- Separate dose from dairy products, antacids, and iron supplements by 2 hours. Swallow whole with plenty of water and remain upright (do not lie down) for an hour after taking doxycycline to prevent oesophageal irritation. Single daily doses are best taken in the morning rather than at night.

Flucloxacillin

ATC code: J01CF05

Capsule, 250 mg, 500 mg LOU 2

Powder for oral liquid, 125 mg/5 mL, LOU 2

Powder for injection, 500 mg vial, LOU 4

Indications and dose

Adult

Infections due to beta-lactamase-producing staphylococci including otitis externa, adjunct in pneumonia, oral: 250–500 mg 4 times a day

by IM injection: 250–500 mg every 6 hours

by slow IV injection, or by IV infusion: 0.25–1 g every 6 hours

Impetigo, oral: 250–500 mg 4 times a day for 5–7 days (higher dose for severe infections)

by IM injection: 250–500 mg every 6 hours

by slow IV injection, or by IV infusion: 0.25–2 g every 6 hours

Cellulitis, Erysipelas, oral: 0.5–1 g 4 times a day for 5–7 days then review

by slow IV injection, or by IV infusion: 1–2 g every 6 hours

Mild diabetic foot infection, oral: 0.5–1 g 4 times a day for 7 days then review

Moderate to severe diabetic foot infection, oral: 1 g 4 times a day

by slow IV injection, or by IV infusion: 1–2 g every 6 hours

Leg ulcer infection, oral: 0.5–1 g 4 times a day for 7 days

by slow IV injection, or by IV infusion: 1–2 g every 6 hours

Endocarditis (in combination with other antibacterial if necessary), by slow IV injection, or by IV infusion: **body weight up to 85 kg:** 8 g daily in 4 divided doses; **body weight 85 kg and above:** 12 g daily in 6 divided doses

Osteomyelitis, by slow IV injection, or by IV infusion: Up to 8 g daily in 3–4 divided doses

Surgical prophylaxis, by slow IV injection, or by IV infusion: 1–2 g, to be administered up to 30 minutes before the procedure, then (oral or by IM injection or by slow IV injection or *by IV infusion*) 500 mg every 6 hours if required for up to 4 further doses in high risk procedures.

Paediatric

Infections due to beta-lactamase-producing staphylococci including otitis externa, Adjunct in pneumonia, oral

Neonate up to 7 days: 25 mg/kg twice daily

Neonate 7 days to 20 days: 25 mg/kg 3 times a day

Neonate 21 days to 28 days: 25 mg/kg 4 times a day

Child 1 month–1 year: 62.5–125 mg 4 times a day

Child 2–9 years: 125–250 mg 4 times a day

Child 10–17 years: 250–500 mg 4 times a day

By IM injection

Child: 12.5–25 mg/kg every 6 hours (max. per dose 500 mg every 6 hours)

By slow IV injection, or By IV infusion.

Neonate up to 7 days: 25 mg/kg every 12 hours.

Neonate 7 days to 20 days: 25 mg/kg every 8 hours.

Neonate 21 days to 28 days: 25 mg/kg every 6 hours.

Child: 12.5–25 mg/kg every 6 hours (max. per dose 1 g every 6 hours)

Impetigo, oral

Neonate up to 7 days: 25 mg/kg twice daily

Neonate 7 days to 20 days: 25 mg/kg 3 times a day

Neonate 21 days to 28 days: 25 mg/kg 4 times a day

Child 1 month–1 year: 62.5–125 mg 4 times a day for 5–7 days

Child 2–9 years: 125–250 mg 4 times a day for 5–7 days

Child 10–17 years: 250–500 mg 4 times a day for 5–7 days

By IM injection

Child: 12.5–25 mg/kg every 6 hours (max. per dose 500 mg every 6 hours)

By slow IV injection, or by IV infusion

Neonate up to 7 days: 25 mg/kg every 12 hours.

Neonate 7 days to 20 days: 25 mg/kg every 8 hours.

Neonate 21 days to 28 days: 25 mg/kg every 6 hours.

Child: 12.5–25 mg/kg every 6 hours (max. per dose 1 g every 6 hours)

Severe infections due to beta-lactamase-producing staphylococci including otitis externa, Adjunct in pneumonia (severe infection), Adjunct in impetigo (severe infection), by slow IV injection, or by IV infusion

Neonate up to 7 days: 50 mg/kg every 12 hours

Neonate 7 days to 20 days: 50 mg/kg every 8 hours

Neonate 21 days to 28 days: 50 mg/kg every 6 hours

Child: 25–50 mg/kg every 6 hours (max. per dose 2 g every 6 hours)

Cellulitis, erysipelas, oral

Child 1 month–1 year: 62.5–125 mg 4 times a day for 5–7 days then review

Child 2–9 years: 125–250 mg 4 times a day for 5–7 days then review

Child 10–17 years: 250–500 mg 4 times a day for 5–7 days then review

By slow IV injection, or by IV infusion

Child: 12.5–25 mg/kg every 6 hours (max. per dose 1 g every 6 hours)

Endocarditis (in combination with other antibacterial if necessary)

By slow IV injection, or by IV infusion

Child: 50 mg/kg every 6 hours (max. per dose 2 g every 6 hours)

Osteomyelitis, by slow IV injection, or by IV infusion

Neonate up to 7 days: 50–100 mg/kg every 12 hours

Neonate 7 days to 20 days: 50–100 mg/kg every 8 hours

Neonate 21 days to 28 days: 50–100 mg/kg every 6 hours

Child: 50 mg/kg every 6 hours (max. per dose 2 g every 6 hours)

Cerebral abscess, staphylococcal meningitis, by slow IV injection, or by IV infusion

Neonate up to 7 days: 50–100 mg/kg every 12 hours.

Neonate 7 days to 20 days: 50–100 mg/kg every 8 hours.

Neonate 21 days to 28 days: 50–100 mg/kg every 6 hours.

Child: 50 mg/kg every 6 hours (max. per dose 2 g every 6 hours)

Staphylococcal lung infection in cystic fibrosis, oral

Child: 25 mg/kg 4 times a day (max. per dose 1 g), alternatively 100 mg/kg daily in 3 divided doses, maximum 4 g per day

By slow IV injection, or by IV infusion.

Child: 50 mg/kg every 6 hours (max. per dose 2 g every 6 hours)

Prevention of Staphylococcus aureus lung infection in cystic fibrosis—primary prevention, oral

Neonate: 125 mg twice daily.

Child 1 month–3 years: 125 mg twice daily

Prevention of Staphylococcus aureus lung infection in cystic fibrosis—secondary prevention, oral

Child: 50 mg/kg twice daily (max. per dose 1 g twice daily)

Contraindications: Hypersensitivity to flucloxacillin and other penicillins. Patient with history of flucloxacillin-associated jaundice/hepatic dysfunction.

Precautions: With IV use accumulation of electrolytes can occur with high doses, risk of kernicterus in jaundiced neonates when high doses given parenterally, patient with spirochaete infections (e.g., syphilis, leptospirosis), history of hypersensitivity to β-lactam antibiotics, newborn infants.

Hepatic impairment: Manufacturer advises caution, including in those with risk factors for hepatic reactions.

Renal impairment: With IV use accumulation of electrolytes can occur in patients with renal failure. Dose adjustments Use normal dose every 8 hours if EGFR less than 10 mL/min/1.73 m2.

Pregnancy: Not known to be harmful.

Breastfeeding: Trace amounts in milk, but appropriate to use.

Adverse effects: General Adverse effects: arthralgia, fever, neutropenia

Specific Adverse effects: Common or very common with oral use GI disorder

with oral use eosinophilia, myalgia with parenteral use bronchospasm, coma, dyspnoea, electrolyte imbalance, erythema nodosum, hallucination. Jarisch-Herxheimer reaction, nephropathy, neurotoxicity,

oral candidiasis, platelet dysfunction, purpura nonthrombocytopenic, vasculitis

Interactions: Allopurinol increases the risk of skin rash when given with penicillins. Penicillins potentially alter the anticoagulant effect of coumarins. Monitor INR and adjust dose. Leflunomide is predicted to increase the exposure to benzylpenicillin. Penicillins are predicted to increase the risk of toxicity when given with methotrexate. Paracetamol potentially increases the risk of high anion gap metabolic acidosis when given with flucloxacillin. Penicillins are predicted to increase the risk of bleeding events when given with phenindione. Concomitant penicillin and aminoglycoside therapy has been reported to result in inactivation of the aminoglycoside. Preferable to separate administration by 1 hour. Bacteriostatic drugs (e.g., chloramphenicol, tetracycline) may interfere with the bactericidal effect of flucloxacillin.

Notes:

- Important safety information: hepatic disorders
- Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors. Manufacturer advises flucloxacillin should not be used in patients with a history of hepatic dysfunction associated with flucloxacillin. Flucloxacillin should be used with caution in patients with hepatic impairment.
- Careful enquiry should be made about hypersensitivity reactions to beta-lactam antibacterials
- **Directions for administration:** With IV use for IV infusion, dilute reconstituted solution in glucose 5% or sodium chloride 0.9% and give intermittently over 30–60 minutes.
- Effect on laboratory tests: False-positive urinary glucose (if tested for reducing substances).

Gentamicin

ATC code: J01GB03

Injection, 10 mg/mL in 2-mL vial/amp, LOU 2

Injection, 40 mg (as sulphate)/mL in 2-mL vial/amp, LOU 3

Indications and dose

Adult

Infections with susceptible organisms, including sepsis, pneumonia, acute pyelonephritis and meningitis, taking local resistance factors into account, by IM injection or slow IV injection (over at least 3 minutes) or IV infusion: 3–5 mg/kg daily in divided doses every 8 hours (for severe infections for 7–10 days)

Pelvic inflammatory disease (with clindamycin) by IV injection: 1.5 mg/kg every 8 hours

Endocarditis (as part of combination therapy), by IM injection or by IV injection (over at least 3 minutes): 1 mg/kg every 8 hours

Surgical prophylaxis (with clindamycin), by IV injection: 5 mg/kg as a single dose at induction

Note: One-hour (peak) concentrations should not exceed 5–10 mg/L (3–5 mg/L for endocarditis); pre-dose (trough) concentration should be <2 mg/L (less than 1 mg/L in endocarditis).

Paediatric

Treatment of infections with susceptible organisms, IV or IM

Term neonate: 3.5–5 mg/kg once daily

Infant or **child under 10 years:** 7.5 mg/kg once daily

Child over 10 years: 6 mg/kg once daily (maximum dose 240–360 mg)

Contraindications: Myasthenia gravis, hypersensitivity to gentamicin and other aminoglycosides.

Precautions: Renal impairment, neonates and infants (use with caution and monitor renal, auditory and vestibular function, and serum gentamicin concentrations), avoid prolonged use, conditions characterized by muscular weakness, obesity (use ideal body weight to calculate dose and monitor serum gentamicin concentration closely). Patients with hypocalcaemia, hypokalaemia, hypomagnesaemia, pre-existing vertigo, tinnitus, or hearing loss, family history of ototoxicity.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Reduce dose frequency. Monitor renal, auditory and vestibular function. Monitor serum gentamicin concentration.

Adverse effects:

- Common: Nephrotoxicity (see below), ototoxicity (see below).
- Rare**:** Hypomagnesaemia, hypokalaemia, hypocalcaemia, anaphylaxis (probably due to sulfites in some formulations), bronchospasm, neuromuscular blockade (see below), oliguria, peripheral neuropathy, antibiotic-associated colitis.
- Nephrotoxicity: Usually reversible and can be anticipated if treatment lasts > 7–10 days, usually presents as gradually worsening non-oliguric renal failure with increasing serum creatinine and proteinuria, but may present as acute tubular necrosis.
- Ototoxicity: Clinically evident vestibular ototoxicity (nausea, vomiting, vertigo, nystagmus, difficulties with gait) and cochlear ototoxicity (noticeable hearing loss, tinnitus, feeling of fullness in ear) have been associated with gentamicin use. As the patient is unaware of the first symptoms of cochlear toxicity, it may appear to begin after stopping treatment. Ototoxicity caused by gentamicin can be irreversible, permanent deafness may occur.
- Neuromuscular blockade may result in respiratory depression, can usually be reversed with prompt administration of IV calcium gluconate, the effect of neostigmine is variable.
- Anaemia, blood dyscrasias, purpura, erythema, pruritus (topical), rash, convulsion, antibiotic-associated colitis, vomiting, nausea, stomatitis.

Interactions: (*indicates serious)

- Amphotericin B: increased risk of nephrotoxicity.
- Capreomycin: increased risk of nephrotoxicity and ototoxicity.
- * Ciclosporin: increased risk of nephrotoxicity.
- Digoxin: possibly increased plasma concentration of digoxin.
- * Furosemide: increased risk of ototoxicity.
- Magnesium sulphate: additive neuromuscular blocking effect with aminoglycosides and parenteral magnesium sulphate, use combinations cautiously, monitor respiratory function.
- * Neostigmine: antagonism of effect of neostigmine.
- Nondepolarizing neuromuscular blockers: aminoglycosides prolong effect of nondepolarizing neuromuscular blockers, may lead to respiratory insufficiency.
- Other nephrotoxic agents: co-administration with other drugs which are ototoxic or nephrotoxic may increase risk of these adverse effects.
- Penicillins and cephalosporins: concomitant penicillin and aminoglycoside therapy has been reported to result in inactivation of the aminoglycoside. Preferable to separate administration by 1 hour.
- * Pyridostigmine: antagonism of effect of pyridostigmine.
- * Suxamethonium: enhanced muscle relaxant effect.
- Vancomycin: increased risk of nephrotoxicity and ototoxicity.
- * Vecuronium: enhanced muscle relaxant effect. May increase hypothrombinanaemic effect of oral anticoagulants.
- Increased risk of hypocalcaemia with bisphosphonates.

Notes:

- In obese or severely oedematous children use the ideal weight for height to calculate dose.
- Dilution and administration: According to the manufacturer's directions.
- Administration For IV infusion, dilute in glucose 5% or sodium chloride 0.9%, infuse over 30–60 minutes. Final concentration of IV administration should not exceed 10 mg/mL.
- Therapeutic drug monitoring: Monitor serum gentamicin concentration and reduce doses or increase dosing intervals, or both, as necessary. Pre-dose ("trough") concentration should be less than 1 mg/L.
- Target serum concentrations may vary depending on indication and institution.

Metronidazole

ATC code: J01XD01

Injection, 500 mg in 100-mL vial, LOU 4

Oral liquid, 40 mg (as benzoate)/mL, LOU 2

Tablet, 400 mg, LOU 2

Indications and dose

Adult

Anaerobic bacterial infections including ulcerative gingivitis, acute oral infections, tetanus, skin and soft tissue infections, and C. difficile infection (oral therapy), surgical prophylaxis, oral: 800 mg initially, then 400 mg every 8 hours

By IV route

500 mg 8 hourly via infusion at a rate of 5 mL/min over 20–60 minutes usually for about 7 days. Max: 4,000 mg daily. Alternatively, 1,000–1,500 mg once daily as single dose. Substitute to oral therapy as soon as possible.

Bacterial vaginosis, oral: 2 g as a single dose or 400–500 mg twice daily for 5–7 days

Pelvic inflammatory disease, oral: 400–500 mg twice daily for 14 days

Leg ulcers and pressure sores, oral: 400 mg every 8 hours for 7 days

Acute ulcerative gingivitis, oral: 200–250 mg every 8 hours for 3 days

Acute oral infections, oral: 200 mg every 8 hours for 3–7 days

Antibiotic-associated colitis, oral: 800 mg initially, then 400 mg 3 times daily for 10 days

Surgical prophylaxis of postoperative anaerobic bacterial infections, oral: 400–500 mg 2 hours before surgery, up to 3 further doses of 400–500 mg may be given every 8 hours for high-risk procedures

By rectum (suppository)

1 g 2 hours before surgery, up to 3 further doses of 1 g may be given every 8 hours for high-risk procedures

By IV infusion (if rectal administration inappropriate)

500 mg at induction, up to 3 further doses of 500 mg may be given every 8 hours for high-risk procedures, alternatively, 1,000–1,500 mg once for 30–60 minutes preoperatively.

Eradication of H. pylori associated with peptic ulcer disease, oral

In combination with another antibacterial and PPI: 400 mg 12 hourly for 7–14 days. In combination with omeprazole and amoxicillin: 400 mg 8 hourly. Consult official guidelines before initiating therapy.
Trichomoniasis, oral: 2,000 mg as a single dose or 200 mg tid for 7 days. Alternatively, 400 mg bid for 5–7 days. Sexual partners should also be treated.

Giardiasis, oral: 2,000 mg once daily for 3 days or 400 mg tid for 5 days or 500 mg bid for 7–10 days. Alternatively, 15–40 mg/kg daily in 2–3 divided doses.

Amoebiasis, oral: 800 mg tid 5 days (intestinal infection), 400–800 mg for 5–10 days (extra-intestinal infection). Alternatively, 35–50 mg/kg daily in 3 divided doses for 5–10 days. Max: 2,400 mg daily.

Paediatric

Anaerobic bacterial infections, oral:

Neonate: Initially 15 mg/kg then 7.5 mg/kg every 12 hours

Infant or **child:** 7.5 mg/kg every 8 hours. Maximum dose 400 mg.

IV infusion:

Neonate: 15 mg/kg as a single loading dose, followed by 7.5 mg/kg every 12 hours starting 24 hours after loading dose.

Infant or **child:** 7.5 mg/kg every 8 hours. Maximum dose 500 mg.

Note: Acute ulcerative gingivitis is usually successfully treated in 3 days, *C. difficile* infection should be treated orally, and is usually treated for 7–10 days, while other anaerobic and oral anaerobic conditions usually treated for only 7 days.

Anaerobic infections, by rectum

Child up to 1 year: 125 mg every 8 hours for 3 days, then every 12 hours

Child 1–5 years: 250 mg every 8 hours for 3 days, then every 12 hours

Child 5–10 years: 500 mg every 8 hours for 3 days, then every 12 hours

Child over 10 years: 1 g every 8 hours for 3 days, then 1 g every 12 hours

Surgical prophylaxis, oral or IV infusion:

Infant or **child:** 7.5 mg/kg 2 hours before surgery. Up to 3 further doses of 7.5 mg/kg may be given every 8 hours for high-risk procedures. Maximum dose 500 mg.

Eradication of H. pylori associated with peptic ulcer disease, oral

Child: In combination with another antibacterial and PPI: 20 mg/kg daily in divided doses for 7–14 days. Max 500 mg 12 hourly.

Trichomoniasis, oral:
Child: 40 mg/kg as single dose or 15–30 mg/kg daily in 2–3 divided doses. Max: 2,000 mg/dose.

Giardiasis, oral
Child 1–3 years: 500 mg once daily for 3 days

Child >3–7 years: 600–800 mg once daily for 3 days

Child >7–10 years: 1,000 mg once daily for 3 days.

Child >10 years: Same as adult dose. Alternatively, 15–40 mg/kg daily in 2–3 divided doses.

Amoebiasis, oral

Child 1–3 years: 200 mg every 8 hours for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection).

Child 3–7 years: 200 mg 4 times daily for 5 days in intestinal infection (for 5–10 days (in extra-intestinal infection).

Child 7–10 years: 400 mg every 8 hours for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection). Alternatively, 35–50 mg/kg daily in 3 divided doses for 5–10 days. Max: 2,400 mg daily.

Contraindications: Hypersensitivity to metronidazole and other nitroimidazoles. Concomitant use with disulfiram within the last 14 days. Coadministration with alcohol or propylene glycol containing products during or 3 days after therapy discontinuation.

Pregnancy: during the 1st trimester in the treatment of trichomoniasis

Precautions: Hepatic impairment, disulfiram-like reaction with alcohol, clinical and laboratory monitoring in courses lasting longer than 10 days.

Skilled tasks: warn patients or caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours. Patients with or history seizure disorder, blood dyscrasias (e.g., agranulocytosis, leukopenia, neutropenia), patients with Cockayne syndrome.

Hepatic impairment: Severe impairment: reduce total daily dose to one-third and give once daily. Use with caution in hepatic encephalopathy.

Renal impairment: Metabolites may accumulate in severe impairment possibly causing adverse effects. Dose adjustment is not usually necessary.

Adverse effects:

- Common: GI intolerance (nausea, abdominal pain, vomiting, diarrhoea), anorexia, metallic taste, CNS effects (e.g., dizziness, headache), thrombophlebitis (IV), furry tongue, glossitis, stomatitis, paraesthesia.
- Rare: Pancreatitis, abnormal liver function tests, jaundice, hepatitis, optic neuritis, thrombocytopenia, CDAD, hypersensitivity reactions (e.g., rash, itch, flushing, fever), anaphylaxis, angioedema, erythema multiforme, SJS, leukopenia, peripheral neuropathy, seizures, darkening of the urine. High-dose and/or prolonged treatment leukopenia is reversible and usually only occurs after prolonged treatment, peripheral neuropathy (usually reversible) and/or CNS toxicity (including seizures) may occur. Erythematous rash, urticaria, dry skin.

Interactions: (*indicates serious)

- Alcohol: disulfiram-like reaction.
- Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).
- Fluorouracil: metabolism of fluorouracil inhibited (increased toxicity).
- Lithium: increased lithium toxicity reported.
- Lopinavir liquid: disulfiram-like reaction.

- Phenobarbital: metabolism of metronidazole accelerated (reduced plasma concentration).
- * Phenytoin: metabolism of phenytoin inhibited (increased plasma phenytoin concentration).
- * Warfarin: enhanced anticoagulant effect. May increase serum concentrations of ciclosporin and busulfan

Notes:

- Well absorbed orally and the IV route is normally reserved for severe infections.
- Oral absorption from the suspension is lower than from the tablets.
- Patients should be advised to swallow tablets whole with water, during or after food, suspension is best taken 1 hour before food (or on an empty stomach).
- Administration For IV infusion, infuse over 20–30 minutes.

Nitrofurantoin

ATC code: J01XE01

Tablet, 100 mg, LOU 3

Oral liquid, 25 mg/5 mL, LOU 3

Indications and dose:

Acute uncomplicated urinary tract infections, oral: 100 mg every 12 hours or 50 mg every 6 hours, with food for 7 days

Severe recurrent urinary tract infection, oral: 100 mg every 6 hours with food for 7 days (reduced to 200 mg daily in divided doses if severe nausea).

Prophylaxis of chronic urinary tract infections, oral: 50–100 mg at night

Prophylaxis of surgical infections, oral: As immediate-release preparation: 50–100 mg once daily, alternatively, 50 mg 4 times daily. As dual-release preparation: 100 mg twice a day. All doses start on the day of the procedure and 3 days thereafter.

Paediatric

Treatment of acute uncomplicated urinary tract infection, oral

Infant or **child over 3 months**: 750 micrograms/kg four times daily for 3–7 days. Maximum dose 100 mg

Prophylaxis of urinary tract infection, oral

Infant or **child over 3 months:** 1 mg/kg at night. Maximum dose 100 mg

Prophylaxis of surgical infections, oral (as immediate-release preparation):
Child >3 months: 1 mg/kg at bedtime

Adverse effects:

- Common: Dose related GI disorders (including nausea and vomiting, anorexia, diarrhoea and abdominal pain), hypersensitivity reactions (including urticaria, rash, sialadenitis, pruritus, angioedema), headache, drowsiness, vertigo, dizziness.
- Rare**:** Peripheral polyneuropathy (see below), cholestatic jaundice, hepatitis, hepatotoxicity (see below), acute and chronic pulmonary reactions (see below), skin reactions including erythema multiforme, SJS, exfoliative dermatitis, lupus-like syndrome, anaphylaxis, drug fever, blood disorders including eosinophilia, arthralgia, pancreatitis, benign intracranial hypertension.
- Hepatotoxicity: Acute hepatocellular or cholestatic reactions generally occur in the first 6 weeks of treatment, sometimes with fever, eosinophilia, rash and are usually reversible. Chronic active hepatitis (sometimes reversible) mostly occurs in women, usually after about 6 months treatment, may be associated with pulmonary toxicity (see below). Both types can be fatal.
- Pulmonary toxicity: Pulmonary fibrosis has been reported. Possible association with lupus erythematosus-like syndrome.
- Peripheral polyneuropathy Begins with peripheral paraesthesia and sensory loss (usually in lower limbs), can progress to motor loss and muscle atrophy. Improvement usually occurs after stopping treatment, but it may be incomplete. The main predisposing factor appears to be renal impairment.

Interactions: (*indicates serious):

- Fluconazole: concurrent use may result in increased risk of hepatic and pulmonary toxicity.
- Norfloxacin: may result in antagonism of the antibacterial effect of norfloxacin.
- Folic acid: concurrent use may result in decreased folic acid serum levels.
- Increased serum level and toxicity and decreased renal excretion with uricosuric drugs (e.g., probenecid, sulfinpyrazone).
- Decreased antimicrobial effect with effects with carbonic anhydrase inhibitors (e.g., acetazolamide). May diminish the therapeutic effect of live polio vaccine.

Notes:

Give with food or milk to reduce nausea and to improve absorption.

Advice Patients and their Caregivers to tell their doctor immediately if they have difficulty breathing, develop a cough or get any numbness or tingling.

Monitoring during long-term treatment monitor the following: pulmonary function, liver function every month for 3 months, then every 3 months, as onset of hepatotoxicity may be insidious, renal function as peripheral polyneuropathy is more likely to occur if this is impaired, for development of paraesthesia as stopping treatment early can prevent severe neuropathy.

Phenoxymethylpenicillin (Penicillin V)

ATC code: J01CE02

Powder for oral liquid, 250 mg (as potassium salt)/5 mL, LOU 3

Tablet, 250 mg (as potassium salt), LOU 3

Indications and dose:

Streptococcal pharyngitis, otitis media, cellulitis, mouth infections, respiratory tract infections post-splenectomy prophylaxis.

Adult

Infections due to sensitive organisms, oral: 125–250 mg 6–8 hourly for 10 days, or 500 mg every 6 hours for lower respiratory tract infections until patient is afebrile for at least 2 days. Increased up to 1 g every 6 hours in severe infections

Secondary prophylaxis of rheumatic fever, oral: 250 mg twice daily

Paediatric

Infections due to sensitive organisms, oral

Child all ages: 10–12.5 mg/kg/dose (maximum 500 mg) every 6 hours. Dose may be doubled in severe infections.

Secondary prophylaxis of rheumatic fever, oral

Child all ages: 10–12.5 mg/kg/dose (maximum 500 mg) twice daily

Contraindications: Hypersensitivity to penicillins, concomitant use with nadolol and propranolol.

Precautions: Patient with history of asthma, seizure disorders, history of β-lactam allergy, infectious mononucleosis (high incidence of rash).

Hepatic impairment: Dosage adjustment may be necessary in patients with impaired liver function when they also have renal failure.

Renal impairment: Dosage adjustment not necessary.

Adverse effects: Common: Diarrhoea, nausea, rash, urticaria, superinfection (including candidiasis) especially during prolonged treatment with broad-spectrum penicillins, allergy. Uncommon: Fever, vomiting, erythema, exfoliative dermatitis, angioedema, CDAD. Rare: Anaphylaxis, bronchospasm, tooth discoloration, joint pains, interstitial nephritis, serum sickness-like syndrome, haemolytic anaemia, neurotoxicity (e.g., seizures with high doses or impaired renal function), coagulation disorders, blood dyscrasias (e.g., neutropenia (related to dose and duration of treatment), thrombocytopenia, nephropathy (with parenteral use), Stevens- Johnson syndrome, toxic epidermal necrolysis.

Interactions: (*indicates serious):

- Aminoglycosides: concomitant penicillin and aminoglycoside therapy has been reported to result in inactivation of the aminoglycoside. Preferable to separate administration by 1 hour.
- Chloramphenicol, erythromycin and tetracyclines: decreased antibacterial effectiveness.
- Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).
- Methotrexate: reduced excretion of methotrexate (increased risk of toxicity).
- Typhoid Live vaccines: decreased immunological response to the typhoid vaccine.
- May interfere with anticoagulant control.
- Potentially Fatal: Increased risk of anaphylactic reactions with nadolol and propranolol.

Notes: Patient advice: Phenoxymethylpenicillin should be taken at least 30 minutes before or 2 hours after food.

Tinidazole

ATC code: J01XD02

Tablet, 500 mg, LOU 2

Indications and dose

Adult

Anaerobic infections, oral: Initially 2 g, followed by 1 g daily usually for 5–6 days, alternatively 500 mg twice daily usually for 5–6 days

Bacterial vaginosis, acute ulcerative gingivitis, oral: 2 g for 1 single dose, may also be given as 2 g for 2 consecutive days or 1 g daily for 5 days for vaginosis

Abdominal surgery prophylaxis, oral: 2 g for 1 single dose, to be administered approximately 12 hours before surgery

Intestinal amoebiasis, oral: 2 g once daily for 2–3 days

Amoebic involvement of liver, oral: 1.5–2 g once daily for 3–6 days

Urogenital trichomoniasis, giardiasis, oral: 2 g for 1 single dose

Helicobacter pylori eradication, oral: 500 mg 12 hourly, given with clarithromycin and omeprazole for 7 days

Paediatric

Intestinal amoebiasis, oral

Child 1 month–11 years: 50–60 mg/kg once daily (max. per dose 2 g) for 3 days

Child 12–17 years: 2 g once daily for 2–3 days

Amoebic involvement of liver, oral

Child 1 month–11 years: 50–60 mg/kg once daily (max. per dose 2 g) for 5 days

Child 12–17 years: 1.5–2 g once daily for 3–6 days

Urogenital trichomoniasis, giardiasis, oral

Child 1 month–11 years: 50–75 mg/kg (max. per dose 2 g) for 1 single dose, dose may be repeated once if necessary

Child 12–17 years: 2 g for 1 single dose, dose may be repeated once if necessary

Precautions:

- Pregnancy manufacturer advises avoid in first trimester.
- Breastfeeding Present in milk—manufacturer advises avoid breastfeeding during and for 3 days after stopping treatment.

Adverse effects: Common or very common: Abdominal pain, appetite decreased, diarrhoea, headache, nausea, skin reactions, vertigo, vomiting, angioedema, ataxia, dizziness, fatigue, flushing, leucopenia, oral

disorders, peripheral neuropathy, seizure, sensation abnormal, taste altered, tongue discolouration, urine discolouration

Potentially fatal: Hypersensitivity

Interactions

Although not specifically identified in studies with tinidazole, the following interactions with other medicines were reported for metronidazole, a chemically-related nitroimidazole. Therefore, these Interactions with other medicines may occur with tinidazole.

Potential Effects of Tinidazole on Other Drugs:

- Warfarin and Other Oral Coumarin Anticoagulants: As with metronidazole, tinidazole may enhance the effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of PT. The dosage of oral anticoagulants may need to be adjusted during tinidazole co-administration and up to 8 days after discontinuation.
- Alcohols, Disulfiram: Alcoholic beverages and preparations containing ethanol or propylene glycol should be avoided during tinidazole therapy and for 3 days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur. Psychotic reactions have been reported in alcoholic patients using metronidazole and disulfiram concurrently. Though no similar reactions have been reported with tinidazole, tinidazole should not be given to patients who have taken disulfiram within the last two weeks.
- Lithium: Metronidazole has been reported to elevate serum lithium levels. It is not known if tinidazole shares this property with metronidazole, but consideration should be given to measuring serum lithium and creatinine levels after several days of simultaneous lithium and tinidazole treatment to detect potential lithium intoxication.
- Phenytoin, Fosphenytoin: Concomitant administration of oral metronidazole and IV phenytoin was reported to result in prolongation of the half-life and reduction in the clearance of phenytoin. Metronidazole did not significantly affect the pharmacokinetics of orally-administered phenytoin.
- Cyclosporine, Tacrolimus: There are several case reports suggesting that metronidazole has the potential to increase the levels of cyclosporine and tacrolimus. During tinidazole coadministration with either of these drugs, the patient should be monitored for signs of calcineurin-inhibitor associated toxicities.
- Fluorouracil: Metronidazole was shown to decrease the clearance of fluorouracil, resulting in an increase in adverse effects without an increase in therapeutic benefits. If the concomitant use of tinidazole and fluorouracil cannot be avoided, the patient should be monitored for fluorouracil-associated toxicities.

Potential Effects of Other Drugs on Tinidazole

CYP3A4 Inducers and Inhibitors: Simultaneous administration of tinidazole with drugs that induce liver microsomal enzymes, i.e., CYP3A4 inducers such as phenobarbital, rifampin, phenytoin, and fosphenytoin (a prodrug of phenytoin), may accelerate the elimination of tinidazole, decreasing the plasma level of tinidazole. Simultaneous administration of drugs that inhibit the activity of liver microsomal enzymes, i.e., CYP3A4 inhibitors such as cimetidine and ketoconazole, may prolong the half-life and decrease the plasma clearance of tinidazole, increasing the plasma concentrations of tinidazole.

Cholestyramine: Cholestyramine was shown to decrease the oral bioavailability of metronidazole by 21%. Thus, it is advisable to separate dosing of cholestyramine and tinidazole to minimize any potential effect on the oral bioavailability of tinidazole.

Oxytetracycline: Oxytetracycline was reported to antagonize the therapeutic effect of metronidazole.

Notes:

- Monitoring requirements: Clinical and laboratory monitoring advised if treatment exceeds 10 days.
- Tinidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa, it has a longer duration of action than metronidazole.

7.2.2. Watch Group Antibiotics

Azithromycin

ATC code: J01FA10

Tablet (scored), 500 mg (anhydrous), LOU 2

Powder for oral liquid, 200 mg/5 mL, LOU 2

Indications and dose

Adult

Uncomplicated genital chlamydial infections, trachoma, oral: **over 45 kg:** 1 g as a single dose, u**nder 45 kg:** 20 mg/kg as a single dose

Streptococcal infection in patients who are allergic to penicillin, oral: 500 mg once daily for 3 days

Respiratory-tract infections, otitis media, skin and soft tissue infections, oral: 500 mg once daily for 3 days, alternatively, 500 mg once daily for 1 day, then 250 mg once daily for 4 days.

Uncomplicated genital chlamydial infections, non-gonococcal urethritis, oral: 1 g for 1 dose

Uncomplicated gonorrhoea, oral: 1 g for 1 dose, in combination with ceftriaxone

Paediatric

Streptococcal infection in patients who are allergic to penicillin, oral

Child 6 months–11 years: 10 mg/kg once daily (max. per dose 500 mg) for 3 days

Child 12–17 years: 500 mg once daily for 3 days

Pharyngitis, tonsillitis

Oral

Child > 2 years: as i/r preparation: 12 mg/kg/day for 5 days

Respiratory-tract infections, otitis media, skin and soft tissue infections, oral

Child 6 months–17 years (body weight 15–25 kg): 200 mg once daily for 3 days.

Child 6 months–17 years (body weight 26–35 kg): 300 mg once daily for 3 days

Child 6 months–17 years (body weight 36–45 kg): 400 mg once daily for 3 days.

Child 6 months–17 years (body weight 46 kg and above): 500 mg once daily for 3 days.

Child 6 months–17 years: 10 mg/kg once daily (max. per dose 500 mg) for 3 days.

Uncomplicated genital chlamydial infections, non-gonococcal urethritis, oral

Child 12–17 years: 1 g for 1 dose

Contraindications: hepatic impairment, hypersensitivity to macrolide antibiotics.

Precautions: Pregnancy and breastfeeding, patients with myasthenia gravis, electrolyte disturbance particularly hypokalaemia and hypomagnesaemia, bradycardia, cardiac arrhythmia, severe cardiac insufficiency, congenital or documented prolongation of QT interval, ventricular tachycardia reported.

Adverse effects: Anorexia, dyspepsia, flatulence, constipation, pancreatitis, syncope, dizziness, headache, drowsiness, agitation, anxiety, hyperactivity, photosensitivity, hepatitis, interstitial nephritis, acute renal failure, asthenia, paraesthesia, arthralgia, convulsions, mild neutropenia, thrombocytopenia, tinnitus, hepatic necrosis, hepatic failure, tongue discoloration, and taste disturbances, myasthenia gravis, deafness Potentially fatal: Rarely, serious hypersensitivity reactions (e.g., anaphylaxis, angioedema, SJS, toxic epidermal necrolysis, acute generalised exanthematous pustulosis drug reaction with eosinophilia and systemic symptoms), fulminant hepatitis leading to liver failure, prolonged cardiac repolarisation and QT interval, cardiac arrhythmia, torsades de pointes, CDAD.

Interactions: Antacids (aluminium hydroxide, magnesium hydroxide) reduce absorption of azithromycin, artemether + lumefantrine avoid concomitant use advised, possible inhibition of metabolism of ciclosporin (increased plasma concentration), oral contraceptive effect of estrogens possibly reduced (risk probably small), increased plasma concentration of digoxin (increased risk of toxicity), plasma concentration of azithromycin possibly increased with ritonavir, possibly enhanced anticoagulant effect of warfarin, increased risk of prolonged QT interval with class IA (e.g., quinidine, procainamide) and class III (e.g., dofetilide, amiodarone, sotalol) antiarrhythmics, pimozide cisapride and terfenadine.

Notes:

» Not to be taken at the same time as aluminium or magnesium containing indigestion remedies. Capsules should be taken at least 1 hour before, or 2 hours after, food, oral suspension can be taken with food.

Cefixime

ATC code: J01DD08

Tablet, 400 mg (as trihydrate), LOU 2

Indications and dose

Adult

Uncomplicated anogenital gonorrhoea, oral: 400 mg as a single dose

Susceptible infections, oral: 200–400 mg daily given as a single dose or in 2 divided doses for 7 days, may be continued for up to 14 days if necessary, depending on the severity of infection.

Paediatric

Susceptible infections

Child >6 months to <10 years weighing <50 kg: 8 mg/kg daily as a single or in 2 divided doses

Contraindications: hypersensitivity to cefalosporins, penicillins or any beta-lactam antibiotics.

Precautions: sensitivity to Beta Lactam antibacterials (avoid if history of immediate hypersensitivity reaction), moderate renal impairment, pregnancy and breastfeeding, use may result in false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test.

Adverse effects: diarrhoea, nausea and vomiting, abdominal discomfort, headache, rarely antibiotic-associated colitis (particularly with higher doses), allergic reactions including rash, pruritus, urticaria, serum sickness-like reactions, fever and arthralgia, and anaphylaxis, erythema multiforme and toxic epidermal necrolysis reported, transient hepatitis, cholestatic jaundice, eosinophilia and blood disorders (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia), reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, hallucinations, confusion, hypertonia, and dizziness, vaginitis, genital pruritus. Potentially Fatal: Drug-induced haemolytic anaemia, acute renal failure including tubulointerstitial nephritis, CDAD, pseudomembranous colitis, SCARs such as toxic epidermal necrolysis, SJS, drug rash with eosinophilia and systemic symptoms, anaphylactic/anaphylactoid reactions including shock.

Interactions: Contraceptive effect of estrogens possibly reduced (risk probably small), Possibly enhanced anticoagulant effect of warfarin. Increased bioavailability for up to 70% with nifedipine. Increased serum concentration with probenecid. May elevate

plasma concentrations of carbamazepine.

Notes: Within the KEML, the use of Cefixime is for syndromic management of sexually transmitted infections only (first line).

Cefotaxime

ATC code: J01DD01

Powder for Injection, 500mg, 1g, LOU 4

Indications and dose

NB: Has been included in the KEML 2023 specifically for management of severe neonatal sepsis in Paediatric patients as per the Basic Paediatric Protocol.

Paediatric

Severe susceptible infections due to sensitive Gram positive and Gram-negative bacteria, Meningitis, by IM, IV injection, or IV infusion:

Neonate up to 7 days: 50 mg/kg every 12 hours.

Neonate 7 days to 20 days: 50 mg/kg every 8 hours.

Neonate 21 days to 28 days: 50 mg/kg every 6–8 hours.

Child: 50 mg/kg every 6 hours; maximum 12 g per day.

Contraindications: Known or suspected hypersensitivity to Cefotaxime or other cephalosporins. Allergic cross-reactions can exist between penicillins and cephalosporins

Precautions: History of allergy or asthma, Serious bullous reactions, *Clostridium difficile* **associated disease (e.g. pseudomembranous colitis),** Neurotoxicity, Haematological reactions e.g. Leucopenia, neutropenia and more rarely, agranulocytosis as well as some case of eosinophilia, thrombocytopenia and haemolytic anaemia,

Hepatic impairment: No dosage adjustment is required.

Renal impairment: Dose adjustments in children: Usual initial dose, then use half normal dose if estimated glomerular filtration rate is less than 5 mL/minute/1.73 m2.

Since Cefotaxime is to a large extent eliminated by haemodialysis, an additional dose should be administered to patients who are dialysed, after the dialysis procedure.

Pregnancy: Not known to be harmful.

Breastfeeding: Present in milk in low concentration, but appropriate to use.

Adverse effects: Uncommon: Drug fever, Jarisch-Herxheimer reaction, renal impairment, seizures. Frequency not known: Arrhythmia (following rapid injection), bronchospasms, encephalopathy, fungal infection, hepatic disorders.

Interactions with other medicines (*indicates serious): Cefotaxime should not be combined with substances having a bacteriostatic action (e.g. tetracycline, erythromycin, chloramphenicol or sulfonamides. An increased risk of oto- and nephrotoxicity has been reported when cefotaxime has been used concomitantly with cephalosporins, aminoglycosides or other nephrotoxic drugs (such as, polymyxin B, colistin) and potent diuretics, (e.g. furosemide) Simultaneous administration of Probenecid leads to higher, more prolonged plasma concentrations of Cefotaxime by interfering with renal tubular transfer thereby delaying excretion.

Ceftazidime

ATC code: J01DD02

Powder for injection, 250 mg or 1 g (as pentahydrate) in vial, LOU 4

Indications and dose

Treatment of susceptible organisms, including S. pyogenes/agalactiae, neisseria, proteus, citrobacter, moraxella, hemophilus

Adult

Broncho-pulmonary infections in cystic fibrosis (persons over 40 kg), IM or IV: 100–150 mg/kg/day, maximum 9 g per day

Febrile neutropenia, nosocomial pneumonia, bacteremia, bacterial meningitis, IM or IV: 2 g every 8 hours

Bone, joint, skin and soft tissue infections, intraabdominal infections, and peritonitis, IM or IV: 2 g every 8 hours

NB: If opting for continuous infusion, then administer 2 g loading dose, then 4 to 6 g every 24 hours

Paediatric

Infections due to sensitive Gram-positive and Gram-negative bacteria, deep IM or IV

Neonate under 7 days: 25–50 mg/kg every 24 hours

Neonate 7–21 days: 25–50 mg/kg every 12 hours

Neonate 21–28 days: 25–50 mg/kg every 8 hours

Child 1 month–18 years: 25–50 mg/kg every 8 hours (maximum 6 g daily). If administering continuous infusion, then a loading dose of 60–100 mg/kg followed by a 100–200 mg/kg/day infusion maximum of 6 g/day.

Contraindications: Cephalosporin hypersensitivity (see section 6.2.1). Previous allergy to Carbapenems, Penicillins or monobactams

Precautions: Sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction,), aztreonam allergy: person may cross-react to ceftazidime, Pregnancy, renal impairment if co-administered with other nephrotoxic drugs, false-positive urinary glucose (if tested for reducing substances) and false-positive Coombs' test, porphyria. Use as a single agent only if susceptibility has been confirmed or is documented.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Reduce dose in mild renal impairment.

Adverse effects:

» Common: Diarrhoea, nausea, rash, electrolyte disturbances, pain and inflammation at injection site, blood dyscrasias (including thrombocytosis and drug-induced eosinophilia), elevations in liver enzymes,

vomiting, headache, dizziness, oral and vaginal candidiasis, CDAD, superinfection, drug fever, leukopenia, neutropenia and thrombocytopenia).

» Rare: Anaphylaxis, bronchial obstruction, urticaria, haemolytic anaemia, angioedema, SJS, toxic epidermal necrolysis, interstitial nephritis, arthritis, serum sickness-like syndrome, neurotoxicity (including seizures), blood dyscrasias (including thrombocytopenia and haemolytic anemia), PT elevations, renal impairment.

Interactions:

» Cephalosporins can cause renal impairment, administration with other drugs which also have this effect may increase risk of nephrotoxicity.

» Aminoglycosides: concomitant cephalosporins and aminoglycoside therapy has been reported to result in inactivation of the aminoglycoside. Preferable to separate administration by 1 hour.

» Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

» Typhoid Live vaccines: decreased immunological response to the typhoid vaccine. Allow 24 hours or more to elapse between the last dose of antibiotic and the administration of oral live typhoid vaccine.

Notes:

» The preferred route of administration is intermittent IV injection or continuous infusion, Deep IM injection only when IV access is impaired.

» Resistant organisms: Enterococcus, listeria, *C. difficile*, Mycoplasma, Legionella, Chlamydia and Bacteroides. Other organisms that commonly acquire resistance include: Klebsiella, Pseudomonas, E. coli, S. aureus, S. pneumoniae, Acinetobacter and Enterobacter.

» IV products are physically incompatible with many substances, avoid mixing with other drugs.

» Carbon dioxide is released during reconstitution, a gas relief needle may be needed to relieve positive pressure.

» Reconstitution and administration: According to manufacturer's directions.

» IM doses over 1 g should be divided between more than one site.

Ceftriaxone

ATC code: J01DD04

Injection IM/IV, 250 mg (as sodium salt) in a vial, LOU 4

Injection IM/IV, 1 g (as sodium salt) in a vial, LOU 4

Indications and dose

Adult

Community-acquired pneumonia, hospital-acquired pneumonia, intra-abdominal infections, complicated urinary-tract infections, acute exacerbations of chronic obstructive pulmonary disease, by IV infusion, or by IV injection, or by deep IM injection: 1–2 g once daily (2 g dose to be used for hospital-acquired pneumonia and severe cases, may be increased to 4 g daily in severe infections, given once or in 2 divided doses via slow IV injection over 5 minutes, or infused over at least 30 minutes)

Cellulitis, erysipelas, moderate diabetic foot infection, severe diabetic foot infection, leg ulcer infection, by IV injection, or by IV infusion: 2 g once daily (In treatment of Lyme disease it is given for 14–21 days, via *slow IV injection* over 5 minutes, or *infused* over at least 30 minutes, or *deep IM injection*)

Complicated skin and soft tissue infections, Infections of bones and joints, by IV infusion, or by IV injection, or by deep IM injection: 2 g once daily

Suspected bacterial infection in neutropenic patients, by IV infusion, or by IV injection, or by deep IM injection: 2–4 g daily, doses at the higher end of the recommended range used in severe cases.

Uncomplicated gonorrhoea and gonococcal conjunctivitis, by deep IM injection: 250–500 mg as a single dose (also used with doxycycline and metronidazole to treat pelvic inflammatory disease).

Disseminated gonococcal infection, by deep IM injection or by IV injection: 1 g daily for 7 days

Surgical prophylaxis, by deep IM injection or by IV injection (over at least 2–4 minutes): 1–2 g at induction

Colorectal surgery (with an antibacterial active against anaerobes), by deep IM injection, by IV injection (over at least 2–4 minutes), or *by IV infusion:* 2 g as a single dose.

Paediatric

Community-acquired pneumonia, hospital-acquired pneumonia, intra-abdominal infections, complicated urinary-tract infections, acute exacerbations of chronic obstructive pulmonary disease, by IV infusion

Neonate up to 15 days: 20–50 mg/kg once daily, doses at the higher end of the recommended range used in severe cases.

Neonate 15 days to 28 days: 50–80 mg/kg once daily, doses at the higher end of the recommended range used in severe cases.

Child 1 month–11 years (body weight up to 50 kg): 50–80 mg/kg once daily, doses at the higher end of the recommended range used in severe cases, maximum 4 g per day.

Child 9–11 years (body weight 50 kg and above): 1–2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases.

Child 12–17 years: 1–2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases.

By IV injection

Child 9–11 years (body weight 50 kg and above): 1–2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases.

Child 12–17 years: 1–2 g once daily: 2 g dose to be used for hospital-acquired pneumonia and severe cases

By deep IM injection

Child 1 month–11 years (body weight up to 50 kg): 50–80 mg/kg daily, doses at the higher end of the recommended range used in severe cases, maximum 4 g per day

Child 9–11 years (body weight 50 kg and above): 1–2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases

Child 12–17 years: 1–2 g once daily: 2 g dose to be used for hospital-acquired pneumonia and severe cases

Cellulitis, erysipelas, moderate diabetic foot infection, severe diabetic foot infection, leg ulcer infection, by IV infusion

Neonate up to 15 days: 20–50 mg/kg once daily, doses at the higher end of the recommended range used in severe cases

Neonate 15 days to 28 days: 50–100 mg/kg once daily, doses at the higher end of the recommended range used in severe cases

Child 1 month–11 years (body weight up to 50 kg): 50–100 mg/kg once daily, doses at the higher end of the recommended range used in severe cases, maximum 4 g per day

Child 9–11 years (body weight 50 kg and above): 2 g once daily

Child 12–17 years: 2 g once daily

By IV injection

Child 9–11 years (body weight 50 kg and above): 2 g once daily

Child 12–17 years: 2 g once daily

By deep IM injection

Child 1 month–11 years (body weight up to 50 kg): 50–100 mg/kg daily, doses at the higher end of the recommended range used in severe cases, maximum 4 g per day

Child 9–11 years (body weight 50 kg and above): 2 g once daily

Child 12–17 years: 2 g once daily

Suspected bacterial infection in neutropenic patients, by IV infusion

Neonate up to 15 days: 20–50 mg/kg once daily, doses at the higher end of the recommended range used in severe cases.

Neonate 15 days to 28 days: 50–100 mg/kg once daily, doses at the higher end of the recommended range used in severe cases.

Child 1 month–11 years (body weight up to 50 kg): 50–100 mg/kg once daily, doses at the higher end of the recommended range used in severe cases, maximum 4 g per day.

Child 9–11 years (body weight 50 kg and above): 2–4 g once daily, doses at the higher end of the recommended range used in severe cases.

Child 12–17 years: 2–4 g once daily, doses at the higher end of the recommended range used in severe cases.

By IV injection

Child 9–11 years (body weight 50 kg and above): 2–4 g once daily, doses at the higher end of the recommended range used in severe cases, doses of 50 mg/kg or more should be given by infusion.

Child 12–17 years: 2–4 g once daily, doses at the higher end of the recommended range used in severe cases.

By deep IM injection

Child 1 month–11 years (body weight up to 50 kg): 50–100 mg/kg daily, doses at the higher end of the recommended range used in severe cases, maximum 4 g per day

Child 9–11 years (body weight 50 kg and above): 2–4 g daily, doses at the higher end of the recommended range used in severe cases.

Child 12–17 years: 2–4 g daily, doses at the higher end of the recommended range used in severe cases.

Bacterial meningitis, Bacterial endocarditis, by IV infusion

Child 1 month–11 years (body weight up to 50 kg): 80–100 mg/kg once daily, 100 mg/kg once daily dose should be used for bacterial endocarditis, maximum 4 g per day.

Child 9–11 years (body weight 50 kg and above): 2–4 g once daily, doses at the higher end of the recommended range used in severe cases.

Child 12–17 years: 2–4 g once daily, doses at the higher end of the recommended range used in severe cases.

By IV injection

Child 9–11 years (body weight 50 kg and above): 2–4 g once daily, doses at the higher end of the recommended range used in severe cases, doses of 50 mg/kg or more should be given by infusion.

Child 12–17 years: 2–4 g once daily, doses at the higher end of the recommended range used in severe cases.

By deep IM injection

Child 1 month–11 years (body weight up to 50 kg): 80–100 mg/kg daily, 100 mg/kg daily dose should be used for bacterial endocarditis, maximum 4 g per day.

Child 9–11 years (body weight 50 kg and above): 2–4 g daily, doses at the higher end of the recommended range used in severe cases.

Child 12–17 years: 2–4 g daily, doses at the higher end of the recommended range used in severe cases.

Neonatal gonococcal conjunctivitis, by IM injection

Neonate: 50 mg/kg as a single dose (maximum: 125 mg) **Contraindications:** hypersensitivity to cephalosporins or history of severe hypersensitivity to other type of β-lactam antibiotic (e.g., penicillins, monobactams, carbapenems), porphyria, premature neonates up to a postmenstrual age of 41 weeks (gestational age and chronological age), term neonates with jaundice, hypoalbuminaemia, acidosis or impaired bilirubin binding.

Precautions: sensitivity to beta lactam antibacterials (avoid if history of immediate hypersensitivity reactions, severe renal impairment, hepatic impairment if accompanied by renal impairment, premature neonates (may displace bilirubin from serum albumin), treatment longer than 14 days, dehydration, or concomitant total parenteral nutrition (TPN) (risk of ceftriaxone precipitation in gallbladder), pregnancy and breastfeeding, may cause false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test, GI disease (e.g., colitis), renal lithiasis, hypercalciuria, impaired vitamin K synthesis or low vitamin K stores. Children.

Adverse effects: diarrhoea, nausea and vomiting, abdominal discomfort, headache, rarely antibiotic-associated colitis (particularly with higher doses), allergic reactions including rash, pruritus, urticaria, serum sickness-like reactions, fever and arthralgia, and anaphylaxis, erythema multiforme and toxic epidermal necrolysis reported, transient hepatitis, cholestatic jaundice, eosinophilia and blood disorders (including thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia), reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, hallucinations, confusion, hypertonia and dizziness, calcium ceftriaxone precipitates in the urine (particularly in the very young, the dehydrated, or in those who are immobilized) or in the gallbladder (consider discontinuation if symptomatic), rarely prolongation of PT and pancreatitis, candida vaginitis.

Interactions: Oral contraceptive effect of estrogens possibly reduced (risk probably small), possibly enhanced anticoagulant effect with warfarin, may increase nephrotoxicity of aminoglycosides. Potentially fatal: Admin with Ca-containing IV solution may cause precipitation of a crystalline material in the lungs and kidneys.

Notes:

- IM doses over 1 g should be divided between more than one site.
- Administer *By IV infusion* over 60 minutes in neonates.

Cefuroxime

ATC code: J01DC02

Powder for injection, 750 mg, LOU 4

Indications and dose

Adult

Surgical prophylaxis: 1.5 g, to be administered up to 30 minutes before the procedure, then (by intravenous injection or by intramuscular injection) 750 mg every 8 hours if required for up to 3 doses (in high risk procedures)

Paediatric

Surgical prophylaxis (initially by intravenous injection)

Child: 50 mg/kg (max. per dose 1.5 g), to be administered up to 30 minutes before the procedure, then (by intravenous injection or by intramuscular injection) 30 mg/kg every 8 hours (max. per dose 750 mg) if required for up to 3 doses (for high-risk

procedures)

Contraindications: History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillin's, monobactams and carbapenems).

Precautions: Hypersensitivity reactions, Severe cutaneous adverse reactions including: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN). Concurrent use of aminoglycosides and diuretics may cause renal impairment. Infections like Colitis and candida infections.

Renal impairment: Dose of 750mg twice daily if eGFR 10–20 mL/minute/1.73m2. Use parenteral dose of 750mg once daily if eGFR less than 10 mL/minute/1.73m2. In children Reduce parenteral dose if estimated glomerular filtration rate less than 20 mL/minute/1.73m2.

Pregnancy: Not known to be harmful

Breastfeeding: Present in milk in low concentrations

Adverse effects: Increased risk of infection, gastrointestinal disorders, fever, Hepatic disorders, Jarisch- Herxheimer reaction, Serum sickness, vasculitis.

Interactions with other medicines (*indicates serious): *Nephrotoxicity, concomitant use of cefuroxime with either aminoglycosides and diuretics may cause renal impairment, concomitant use with oral anticoagulants may give rise to increased international normalized ratio (INR).

Ciprofloxacin

ATC code: J01MA02

Injection: 400mg, LOU 5

Tablet scored, 500 mg (as HCl), LOU 4

Indications and dose

Treatment of infections due to susceptible organisms including pseudomonas, cholera, shigellosis, campylobacter, typhoid and gonorrhoea. Local resistance patterns need to be taken into account

before commencement of therapy.

Adult

Infections due to susceptible organisms, oral: 500–750 mg twice daily

by intravenous infusion: 400 mg every 8–12 hours, to be given over 60 minutes

Chronic sinusitis, chronic suppurative otitis media and malignant otitis externa, oral: 500–750 mg twice daily

Shigellosis, oral: 500 mg twice daily for 3 days

Cholera, oral: 1 g as a single dose

Acute uncomplicated cystitis, oral: 250–500 mg twice daily for 3 days

by intravenous infusion: 400 mg every 8–12 hours, to be given over 60 minutes

Gonorrhoea and gonococcal conjunctivitis, oral: 500 mg as a single dose

Chancroid, oral: 500 mg twice daily for 3 days

Pelvic inflammatory disease, oral: 500 mg twice daily

Pseudomonal lower respiratory tract infection in cystic fibrosis, oral: 750 mg twice daily

Surgical prophylaxis, oral: 750 mg, 60–90 minutes before procedure

Prophylaxis of meningococcal meningitis, oral: 500 mg as a single dose

Prophylaxis, post-inhalational anthrax, oral: 500 mg twice daily for 60 days from confirmed exposure.

by intravenous infusion: 400 mg every 12 hours, to be given over 60 minutes

Paediatric

Complicated urinary tract infection, oral

Child: 10 mg/kg twice daily. Dose may be doubled in severe infections. Maximum dose 750 mg twice daily.

by intravenous infusion:

Neonate: 6 mg/kg every 12 hours, to be given over 60 minutes.

Child: 6 mg/kg every 8 hours; increased to 10 mg/kg every 8 hours (max. per dose 400 mg), in severe infection

Severe respiratory tract infections, GI infections, oral

Child: 20 mg/kg twice daily. Maximum dose 750 mg twice daily

by intravenous infusion:

Neonate: 10 mg/kg every 12 hours, to be given over 60 minutes.

Child: 10 mg/kg every 8 hours (max. per dose 400 mg), to be given over 60 minutes

Pseudomonal lower respiratory tract infection in cystic fibrosis, oral

Child: 20 mg/kg twice daily. Maximum dose 750 mg twice daily

by intravenous infusion:

Child: 10 mg/kg every 8 hours (max. per dose 400 mg), to be given over 60 minutes

Treatment and post-exposure prophylaxis of anthrax, oral

Child 15 mg/kg twice daily. Maximum 500 mg twice daily

by intravenous infusion

Child: 10 mg/kg every 12 hours (max. per dose 400 mg)

Contraindications: History of tendon disorders related to quinolone use, pregnancy, breastfeeding.

Precautions: History of epilepsy, conditions that predispose to seizures, G6PD deficiency, myasthenia gravis, avoid exposure to excessive sunlight (discontinue if photosensitivity occurs), tendon damage, renal impairment, avoid excessive alkalinity of urine and ensure adequate fluid intake as risk of crystalluria. The drug should be discontinued if psychiatric, neurological or hypersensitivity reactions, including severe rash, occur.

Skilled tasks: warn patient or caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment. Health care workers should be aware that the risk of tendon rupture is increased by the concomitant use of corticosteroids, if tendinitis is suspected, the quinolone should be discontinued immediately.

WARNING: Achilles' tendinitis and tendon rupture have been reported with fluoroquinolones in patients of all ages. Tendon rupture may occur within 48 hours of starting treatment. Health care workers should be aware that the risk of tendon rupture is increased by the concomitant use of corticosteroids, if tendinitis is suspected, the quinolone should be discontinued immediately

Renal impairment: Reduce dose if CrCl < 30 mL/min.

Adverse effects:

- Common rash, itch, GI intolerance (nausea, vomiting, dyspepsia, diarrhoea, abdominal pain), metallic taste, headache, dizziness, insomnia, depression, restlessness, tremors, arthralgia, arthritis, myalgia, tendinitis, raised liver enzymes, erythema, pain or thrombophlebitis at IV infusion site.
- Rare: Interstitial nephritis, blood dyscrasias (including agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, methaemoglobinaemia, pancytopenia and thrombocytopenia), orofacial dyskinesia, disturbances in vision, transient hearing impairment, movement disorders, seizures, psychotic reactions, peripheral oedema, angioedema, anaphylaxis, *C. difficile* infection, tendon inflammation and rupture, vasculitis, crystalluria, renal failure, pancreatitis,

hepatitis, cholestatic jaundice, peripheral neuropathy, photosensitivity, fixed drug eruption, erythema multiforme, SJS, toxic epidermal necrolysis, Jarisch-Herxheimer reaction, hyperglycaemia, blood coagulation disorder.

Interactions: (*indicates serious):

- Antacids (aluminium hydroxide, magnesium hydroxide): reduced absorption of ciprofloxacin.
- * Artemether + lumefantrine: manufacturer of artemether with lumefantrine advises to avoid concomitant use.
- Calcium salts: reduced absorption of ciprofloxacin.
- * Ciclosporin: increased risk of nephrotoxicity.
- Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).
- Dairy products: reduced absorption of ciprofloxacin.
- Ferrous salts: absorption of ciprofloxacin reduced by oral ferrous salts.
- *ibuprofen: possibly increased risk of seizures.
- Methotrexate: increased methotrexate concentration and risk of toxicity when high-dose methotrexate is given, monitor methotrexate concentration carefully as increased rescue treatment with calcium folinate may be needed.
- Morphine: manufacturer of ciprofloxacin advises to avoid premedication with morphine (reduced plasma ciprofloxacin concentration) when ciprofloxacin used for surgical prophylaxis.
- Phenytoin: plasma phenytoin concentration can be increased or decreased by ciprofloxacin.
- Theophylline: may result in increased plasma levels of theophylline and significant adverse effects.
- Thyroid hormones: ciprofloxacin may interfere with absorption of thyroxine, resulting in hypothyroidism, separate drug administration times during a long ciprofloxacin course, and monitor thyroid function.
- * Warfarin: enhanced anticoagulant effect.
- Zinc sulphate: reduced absorption of ciprofloxacin.

Notes:

- Avoid monotherapy and always rely on local resistance patterns prior to initiation of therapy.
- Best taken on an empty stomach. Separate doses from iron, antacids and milk by 2 hours. Use water not dairy to swallow.
- Important to maintain an adequate fluid intake.
- Can cause photosensitivity. Use sunscreen, wear protective clothing and a hat.

Clarithromycin

ATC code: J01FA09

Tablet, scored 500 mg, LOU 4

Indications and dose

Adult

Mild diabetic foot infection, oral: 500 mg twice daily for 7 days then review

Leg ulcer infection, oral: 500 mg twice daily for 7 days

Cellulitis, erysipelas, oral: 500 mg twice daily for 5–7 days then review (review after 7 days if infection near the eyes or nose)

Impetigo, oral: 250 mg twice daily for 5–7 days, increased if necessary to 500 mg twice daily, increased dose used in severe infections

Community-acquired pneumonia, oral: 500 mg twice daily for 5 days

Respiratory-tract infections, mild to moderate skin and soft-tissue infections, oral: 250 mg twice daily usually for 7–14 days, increased to 500 mg twice daily, if required in severe infections OR 500 mg once daily usually for 7–14 days, increased to 1 g once daily, if required in severe infections

Acute exacerbation of chronic obstructive pulmonary disease, oral: 500 mg twice daily for 5 days

Acute exacerbation of bronchiectasis, oral: 500 mg twice daily for 7–14 days

Acute cough (if systemically very unwell or at higher risk of complications), acute sore throat, oral: 250–500 mg twice daily for 5 days

Acute otitis media, oral: 250 mg twice daily usually for 7–14 days increased to 500 mg twice daily, if required in severe infections

Prevention of pertussis, oral: 500 mg twice daily for 7 days

H. pylori *eradication (in combination with other medicines – proton pump inhibitor + metronidazole/ amoxicillin), oral:* 500 mg twice daily for 7 days for first- and second-lin e eradication therapy, 10 days for third-lin e eradication therapy

Acute sinusitis, oral: 500 mg twice daily for 5 days

Paediatric

Cellulitis, erysipelas, oral (f/c tablets not recommended for children under 11 years)

Child 12–17 years: 250–500 mg twice daily for 5–7 days then review (review after 7 days if infection near the eyes or nose)

Impetigo, oral

Child 12–17 years: 250 mg twice daily for 5–7 days, increased if necessary to 500 mg twice daily, increased dose used in severe infections

Community-acquired pneumonia

Child 12–17 years: 250–500 mg twice daily for 5 days

Hospital-acquired pneumonia, oral

Child 12–17 years: 500 mg twice daily for 5 days then review

Respiratory-tract infections, Mild to moderate skin and soft-tissue infections, oral

Child 12–17 years: 250 mg twice daily usually for 7–14 days, increased to 500 mg twice daily, if required in severe infections OR 500 mg once daily usually for 7–14 days, increased to 1 g once daily, if required in severe infections

Acute exacerbation of bronchiectasis, oral

Child 12–17 years: 250–500 mg twice daily for 7–14 days

Acute cough (if systemically very unwell or at higher risk of complications), acute sore throat, oral

Child 12–17 years: 250–500 mg twice daily for 5 days

Acute otitis media, oral

Child 12–17 years: 250–500 mg twice daily for 5–7 days

Prevention of pertussis, oral

Child 12–17 years: 500 mg twice daily for 7 days

H. pylori *eradication in combination with omeprazole, and amoxicillin or metronidazole, oral*

Child 12–17 years: 500 mg twice daily

Acute sinusitis, oral

Child 12–17 years: 250 mg twice daily for 5 days, alternatively 500 mg twice daily for 5 days

Contraindications: Previous history of QT prolongation, patient on statins and those with hypomagnesemia or hypokalemia.

Hepatic Impairment: Manufacturer advises caution, avoid in severe failure if renal impairment also present.

Renal Impairment: Avoid if severe hepatic impairment also present.

Pregnancy: Avoid, particularly in the first trimester, unless potential benefit outweighs risk.

Breastfeeding: Avoid unless potential benefit outweighs risk—present in milk.

Adverse effects: Common: abdominal pain, nausea, diarrhea, vomiting, dysgeusia, insomnia and rash. Uncommon: Burping, dry mouth, muscle complaints, oral disorders, thrombocytosis, tremor. Frequency not known: Abnormal dreams, agranulocytosis, depersonalization, depression, mania, Myopathy, psychotic disorder, Renal failure, tooth and urine discolouration. Specific Adverse effects with oral use – Epistaxis; With parenteral use - Cardiac arrest, dyskinesia, haemorrhage, loss of consciousness, pulmonary embolism

Interactions:

» Disopyramide, Quinidine: There have been postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. ECGs should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum concentrations of these medications should also be monitored. There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with disopyramide and quinidine.

» There have been postmarketing reports of hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore, blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

» Digoxin: Digoxin is a substrate for P-glycoprotein (Pgp) and clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are coadministered, inhibition of Pgp by clarithromycin may lead to increased exposure of digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have been reported in postmarketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Monitoring of serum digoxin concentrations should be considered, especially for patients with digoxin concentrations in the upper therapeutic range.

» Oral anticoagulants: Spontaneous reports in the postmarketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. PTs should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously

» Carbamazepine: Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered. Increased serum concentrations of carbamazepine were observed in clinical trials with clarithromycin. There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with carbamazepine.

» Itraconazole: Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, potentially leading to a bi-directional drug interaction when administered concomitantly (see also Itraconazole under "Drugs That Affect Clarithromycin" in the table below). Clarithromycin may increase the plasma concentrations of itraconazole. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged adverse reactions

» Colchicine: Colchicine is a substrate for both CYP3A and the efflux transporter, Pgp. Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. The dose of colchicine should be reduced when co-administered with clarithromycin in patients with normal renal and hepatic function.

- Quetiapine: Quetiapine is a substrate for CYP3A4, which is inhibited by clarithromycin. Coadministration with clarithromycin could result in increased quetiapine exposure and possible quetiapine related toxicities. There have been postmarketing reports of somnolence, orthostatic hypotension, altered state of consciousness, neuroleptic malignant syndrome, and QT prolongation during concomitant administration. Refer to quetiapine prescribing information for recommendations on dose reduction if coadministered with CYP3A4 inhibitors such as clarithromycin.
- Zidovudine: Simultaneous oral administration of clarithromycin immediate-release tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Administration of clarithromycin and zidovudine should be separated by at least two hours. The impact of co-administration of clarithromycin extended-release tablets or granules and zidovudine has not been evaluated.
- Verapamil: Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil.
- Nifedipine: Nifedipine is a substrate for CYP3A. Clarithromycin and other macrolides are known to inhibit CYP3A. There is potential of CYP3A-mediated interaction between nifedipine and clarithromycin. Hypotension and peripheral edema were observed when clarithromycin was taken concomitantly with nifedipine
- Cyclosporine: There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with cyclosporine.
- Tacrolimus: There have been spontaneous or published reports of CYP3A based interactions of clarithromycin with tacrolimus.
- Sildenafil, Tadalafil, Vardenafil: Each of these phosphodiesterase inhibitors is primarily metabolized by CYP3A, and CYP3A will be inhibited by concomitant administration of clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil, or vardenafil will result in increased exposure of these phosphodiesterase inhibitors. Co-administration of these phosphodiesterase inhibitors with clarithromycin is not recommended. Increased systemic exposure of these drugs may occur with clarithromycin, reduction of dosage for phosphodiesterase inhibitors should be considered.
- Theophylline: Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range.
- Midazolam: When oral midazolam is coadministered with clarithromycin, dose adjustments may be necessary and possible prolongation and intensity of effect should be anticipated [see Warnings and Precautions (5.4) and Pharmacokinetics (12.3)].
- Triazolam, Alprazolam: Caution and appropriate dose adjustments should be considered when triazolam or alprazolam is co-administered with clarithromycin. There have been postmarketing reports of Interactions with other medicines and CNS effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.
- Rifabutin: Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis

Notes:

- Use only in combination medicine regimens for treatment of H. pylori infection in adults

Clindamycin

ATC code: J01FF01

Capsule, 150 mg (as HCl), LOU 4

Injection, 150 mg (as phosphate)/mL (2 mL vial), LOU 4

Oral liquid, 15 mg/mL, LOU 4

Indications and dose

Treatment of infections with susceptible anerobic organisms where there is allergy to penicillin and resistance to first-line drugs, including staphylococcal bone and joint infections, peritonitis, and pneumonia. Because of its coverage against Gram-positive aerobes and anaerobes, co-administration with agent covering Gram-negative aerobes is essential. Susceptibility testing before use for methicillin-resistant *Staphylococcus aureus* (MRSA) is important.

Adult

Osteomyelitis or peritonitis (severe infections), oral: 150–300 mg every 6 hours, up to 450 mg every 6 hours

Life-threatening infections: 0.6–2.7 g daily in 2–4 divided doses, increased up to 4.8 g daily (single doses over 600 mg should be given *by IV infusion* only, single doses given *by IV infusion* should not exceed 1.2 g)

Pelvic inflammatory disease, by IV infusion: 900 mg every 8 hours

Endocarditis prophylaxis (for procedures under local or no anaesthetic), oral: 600 mg, 1 hour before procedure

Endocarditis prophylaxis (for procedures under general anaesthetic) by IV infusion: 300 mg over at least 10 minutes, at induction or 15 minutes before procedure, followed by 150 mg 6 hours later oral or by IV infusion

Paediatric

Staphylococcal bone and joint infections (such as Osteomyelitis), Peritonitis, Intra-abdominal sepsis, Methicillin-resistant Staphylococcus aureus (MRSA) in bronchiectasis, bone and joint infections, and skin and soft-tissue infections, oral

Neonate under 14 days: 3–6 mg/kg three times daily

Neonate 14–28 days: 3–6 mg/kg four times daily.

Infant or **child:** 3–6 mg/kg four times daily (body weight under 10 kg, minimum dose 37.5 mg three times daily). Maximum dose 450 mg four times daily

IV infusion or *deep IM injection*

Infant or **child:** 3.75–6.25 mg/kg four times daily, increased up to 10 mg/kg four times daily in severe infections; total daily dose may alternatively be given in three divided doses; in life threatening infection, up to 1.2 g four times daily may be used; single doses over 600 mg must be given by IV infusion.

Contraindications: Diarrhoeal states, avoid injections containing benzyl alcohol in neonates, porphyria and breastfeeding.

Precautions: Antibiotic-associated colitis (*C. difficile* infection) may be fatal, discontinue treatment immediately if diarrhoea develops. In case of allergic reactions use steroids, epinephrine or antihistamines, dialysis usually ineffective, hepatic impairment, renal impairment, monitor liver and renal function on prolonged therapy and in neonates and infants, avoid rapid IV administration, avoid taking with antidiarrhoeal medication, Pregnancy.

Renal impairment: Severe impairment: reduce dose.

Hepatic impairment: Severe impairment: reduce dose.

Adverse effects:

- Common: Diarrhoea (mild to severe: discontinue treatment), nausea, vomiting, abdominal discomfort, rash, pruritus, urticaria. Antibiotic-associated colitis (*C. difficile* infection).
- Rare: Taste disturbance, oesophagitis, anaphylaxis (often related to the tartrazine in the capsule preparation), blood dyscrasias (neutropenia, eosinophilia, agranulocytosis and thrombocytopenia), polyarthritis, jaundice and altered liver function tests, hepatotoxicity (with high doses), SJS, exfoliative and vesiculobullous dermatitis, toxic epidermal necrolysis ("slow" red man syndrome).
- With IV: Hypotension, cardiac arrest (rapid injection), thrombophlebitis.
- With IM: Pain, induration, sterile abscess.

Interactions:(*indicates serious):

Neostigmine: antagonism of effects of neostigmine, Pyridostigmine: antagonism of effects of pyridostigmine, * Suxamethonium: enhanced effects of suxamethonium, * Vecuronium: enhanced muscle relaxant effect.

Notes:

- Clindamycin is a complementary drug when penicillin is not appropriate.
- Consider the necessity for IV administration as adequate levels can be achieved using oral formulations due to high bioavailability.
- Advise patients to discontinue immediately and contact doctor if diarrhoea develops (due to risk of colitis)
- Capsules should be swallowed with a glass of water.
- Administration advice: For IV infusion, dilute in glucose 5% or sodium chloride 0.9% to concentration not > 12 mg/mL and infuse slowly IV over 30–40 minutes to reduce risk of adverse cardiac effects (hypotension, cardiac arrest).

Co-Trimoxazole (Sulfamethoxazole + Trimethoprim)

ATC code: J01EE01

Injection, 80 mg + 16 mg/mL in 5 mL amp, LOU 4

Oral liquid, 40 mg + 8 mg/mL, LOU 2

Tablet, scored, 800 mg + 160 mg, LOU 2

Indications and dose

Use restricted to prophylaxis against selected opportunistic infections in patients with HIV, treatment of Pneumocystis jirovecii pneumonia, and infection with Stenotrophomonas (Xanthomonas) maltophilia

Adult

Treatment of Pneumocystis jirovecii pneumonia, oral: Sulfamethoxazole, up to 100 mg/kg daily + trimethoprim, up to 20 mg/kg daily in 2–4 divided doses for 14–21 days

By IV infusion

Sulfamethoxazole, up to 100 mg/kg daily + trimethoprim, up to 20 mg/kg daily in 2–4 divided doses for 14–21 days

There is no therapeutic advantage of using IV over oral formulations unless the patient cannot take orally.

Prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) pneumonia/toxoplasmosis: Sulfamethoxazole 800 mg + trimethoprim 160 mg, or sulfamethoxazole 400 mg + trimethoprim 80 mg if higher dose not tolerated

Paediatric

NB: Doses are expressed in terms of the trimethoprim component

Treatment of P. jirovecii (P. carinii) infections, oral or *IV*

Infant or **child over 1 month**: 10 mg/kg every 12 hours for 14–21 days. Total daily dose may alternatively, be given in 3–4 divided doses. The IV route is preferred.

Prophylaxis for P. jirovecii (P. carinii) infections (same for toxoplasmosis), oral: 2.5–5 mg/kg.

Infant or **child under 6 months**: 20 mg once daily

Child 6 months–5 years: 40 mg once daily

Child 6–12 years: 80 mg once daily

Contraindications: Hypersensitivity to sulfonamides or trimethoprim, porphyria, megaloblastic anaemia, severe renal impairment, drug induced thrombocytopenia, severe hepatic impairment and children under 6 weeks.

Precautions: Mild to moderate renal impairment, maintain adequate fluid intake (to avoid crystalluria), avoid in blood disorders (unless under specialist supervision), monitor blood counts if on prolonged treatment, discontinue immediately if blood disorder develops, rash (discontinue immediately), predisposition to folate deficiency, asthma, G6PD

deficiency, jaundiced neonates.

Hepatic impairment: Severe impairment: avoid use.

Renal impairment:

- Severe impairment: avoid use.
- Moderate impairment: use half normal dose.
- Plasma monitoring may be required with high doses in renal impairment, seek expert advice.

Adverse effects: Some adverse effects may be hypersensitivity reactions (see below).

Incidence of some adverse effects (rash, fever, nausea, neutropenia, thrombocytopenia, raised hepatic aminotransferases) is substantially higher in patients with AIDS.

Common: Fever, nausea, vomiting, diarrhoea, anorexia, rash, itch, stomatitis, hyperkalaemia, thrombocytopenia, photosensitivity.

Headache, drowsiness, blood disorders (including neutropenia, leukopenia, thrombocytopenia, eosinophilia, megaloblastic anaemia, methaemoglobinaemia).

Rare: Erythema, vasculitis, hyponatraemia, hypoglycaemia, pancreatitis, hepatitis, jaundice, hepatic necrosis, crystalluria, urinary obstruction with anuria/oliguria, lowered mental acuity, depression, tremor, ataxia (after IV use in HIV patients), antibiotic-associated colitis, CDAD, aseptic meningitis.

Hypersensitivity: May present with fever, dyspnoea, cough, rash, eosinophilia, the most serious effects include anaphylaxis, SJS, toxic epidermal necrolysis, serum sickness-like syndrome, lupus like syndrome, pneumonitis, hepatitis, interstitial nephritis, systemic vasculitis and pancytopenia.

Interactions:(*indicates serious):

- Trimethoprim is a folate antagonist and will add to the effects on bone marrow of other folate antagonists, e.g., pyrimethamine.
- Trimethoprim can cause hyperkalaemia, administration with potassium supplements or other drugs which also cause potassium retention can further increase potassium concentration.
- Trimethoprim with sulfamethoxazole can cause nephrotoxicity, giving with other nephrotoxic drugs may cause additional renal adverse effects.
- * Azathioprine: increased risk of haematological toxicity.
- * Ciclosporin: increased risk of nephrotoxicity, plasma ciclosporin concentration possibly reduced by IV trimethoprim.
- * Dapsone: plasma concentration of both dapsone and trimethoprim may increase with concomitant use.
- Digoxin: plasma concentration of digoxin possibly increased.
- Lamivudine: plasma concentration of lamivudine increased (avoid concomitant use of high-dose sulfamethoxazole + trimethoprim).
- * Mercaptopurine: increased risk of haematological toxicity.
- * Methotrexate: antifolate effect of methotrexate increased (avoid concomitant use), risk of methotrexate toxicity increased.
- * Phenytoin: antifolate effect and plasma phenytoin concentration increased.
- Procainamide: increased plasma procainamide concentration.
- * Pyrimethamine: increased antifolate effect.
- * Sulfadoxine + pyrimethamine: increased antifolate effect.
- Thiopental: enhanced effects of thiopental.
- * Warfarin: enhanced anticoagulant effect.

Notes:

- Oral dose is best given with or after food.
- Attention should be paid to the folate status of the patient should treatment be prolonged/ high dose or in patients with pre-existing deficiencies.
- Dilution and administration: For intermittent IV infusion may be further diluted in glucose 5% and 10% or sodium chloride 0.9% or Ringer's IV solution. Must be further diluted, dilute each 5 mL of injection solution to 125 mL. Infuse over 60–90 minutes (but may be adjusted according to fluid requirements). If fluid restriction necessary, 5 mL may be diluted with 75 mL of glucose 5% and the required dose infused over a maximum of 60 minutes. Check container for haze or precipitant during administration. In severe fluid restriction may be given undiluted via a central venous line.

Erythromycin

ATC code: J01FA01

Tablet, 250mg, 500 mg, LOU 3

Indications and dose

Adult

Susceptible respiratory tract infections, skin and oral infections and campylobacter enterititis: 250-500mg mg four times daily. Severe infections up to 1g four times a day

Impetigo/secondary bacterial infection of exczema: 250-500mg four times a day for 5 -7 days

Cellulitis/erysipelas: 500mg four times a day for five to seven day the review

Prevention of recurrent cellulitis/erysipelas (specialist use only): 250mg twice daily

Mild diabetic foot infection: 500mg four times a day for seven day then review

Leg ulcer infection: 500mg four times a day for seven days

Community acquired pneumonia: 500mg four times a day for five days

Acute pharyngitis: 250-500mg four times a day for five days

Early syphilis: 500mg four times a day for fourteen days

Uncomplicated genital chlamydia/ non gonococcal urethritis: 500mg two times a day for fourteen days

Chronic prostatitis: 250-500mg four times a day(up to 4g daily in divided doses in severe infections)

Prevention of secondary case of diphtheria in none immune patients: 500mg every six hours for seven days, treat for further 10 days if nasopharyngeal swab is positive after first seven days of treatment

Rosacea: 500mg twice daily for 6-12 weeks and the doses are repeated intermittently

Acne: 500mg twice daily

Gastrointestinal stasis: 250-500mg three times a day for up to four weeks (to be taken before food)

Prophylaxis of intrauterine infection (in preterm pre-labor rapture of membrane): 250mg four times a day up to 10 day or until established labor whichever is sooner

Paediatric

Susceptible respiratory tract infections, skin and oral infections and campylobacter enteritis

Child 1–23 months: 125mg four times a day. Severe infections four times a day

Child 2–7years: 250mg four times a day. Severe infections 400mg four times a day

Child 8–17 years: 250-500mg four times a day. Severe infection 500-1000mg four times a day

Impetigo/secondary bacterial infection of eczema

Child 8–17 years; 250-500mg four time a day for 5-7 days

Community acquired pneumonia

Child 8–17 years; 250-500mg four times a day for five days

Cellulitis/erysipelas

Child 8–17 years; 250-500mg four time a day for 5-7 days then review

Acute otitis media

Child 8–17 years; 250-500mg four time a day for 5-7 days

Prevention and treatment of pertussis

Child 1–23 months; 125mg four times a day, severe infections up

to 250mg four times a day

Child 2–7 years; 250mg four times a day, severe infections up to 500mg four times a day

Child 8–17 years; 250mg-500mg four times a day, severe infections up to 1000mg four times a day

Contraindications: Hypersensitivity to erythromycin, patients with a history of QT prolongation or ventricular cardiac arrythmia, patients with electrolyte disturbances (hypokalemia, hypomagnesemia), myasthenia gravis,

Precautions: Pseudomembranous colitis, Prolongation of QT interval imparting a risk of developing cardiac arrythmias and torsade de pointes , neonates in first 14 days of life.

Hepatic impairment: use with caution

Renal impairment: consider dose reduction in moderate to severe impairment

Pregnancy: Use only if potential benefit outweighs, risk of cardiovascular malformations in the first trimester.

Breastfeeding: Only small amounts in milk not known to be harmful, use with caution.

Adverse effects: Pseudomembranous colitis, eosinophilia, hypersensitivity reactions, hallucinations, seizures, confusion and vertigo, mitochondria optic neuropathy, deafness(reversible), tinnitus, reversible hearing loss, torsade's de pointes, cardiac arrythmias, cardiac arrest, ventricular fibrillation, hypotension, infantile hypertrophic pyloric stenosis, pancreatitis, diarrhea, anorexia, upper abdominal discomfort, nausea, vomiting, hepatitis, jaundice, SJS (Steven Johnson syndrome), TEN (Toxic epidermal necrolysis), erythema multiforme, angioedema, urticaria, exanthema, interstitial nephritis, fever, increased liver enzymes, pruritis.

Interactions with other medicines (*indicates serious): Use with caution with medicines causing QT prolongation (hydroxychloroquine and chloroquine). Rhabdomyolysis when used with statins. Simvastatin, tolterodine, mizolastine, amisulpride, astemizole, terfenadine, domperidone, cisapride and pimozide. Drugs that induce CYP3A4 (such as rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort)

Piperacillin With Tazobactam

ATC code: J01CR05

Powder for injection, 4 g + 500 mg as sodium salt vial, LOU 5

Indications and dose

Adult

Hospital-acquired pneumonia; sepsis; complicated infections involving the urinary-tract, skin, and soft tissues; acute exacerbation of chronic obstructive pulmonary disease and bronchiectasis; moderate and severe diabetic foot infection; leg ulcer infection, IV infusion: 4.5 g every 8 hours

Neutropenia, severe pneumonia by IV infusion: 4.5 g every 6 hours.

Paediatric

Hospital-acquired pneumonia, septicaemia, complicated infections involving the urinary-tract, complicated infections involving the skin, complicated infections involving the soft-tissues, by IV infusion

Neonate: 90 mg/kg every 8 hours.

Child 1 month–11 years: 90 mg/kg every 6–8 hours (max. per dose 4.5 g every 6 hours)

Child 12–17 years: 4.5 g every 8 hours, increased if necessary to 4.5 g every 6 hours, increased frequency may be used for severe infections

Complicated intra-abdominal infections, by IV infusion

Child 2–11 years: 112.5 mg/kg every 8 hours (max. per dose 4.5 g)

Child 12–17 years: 4.5 g every 8 hours, increased if necessary to 4.5 g every 6 hours, increased frequency may be used for severe infections

Acute exacerbation of bronchiectasis, by IV infusion

Child 1 month–11 years: 90 mg/kg every 6–8 hours (max. per dose 4.5 g every 6 hours)

Child 12–17 years: 4.5 g every 8 hours, increased if necessary to 4.5 g every 6 hours, increased frequency may be used for severe infections

Infections in neutropenic patients, by IV infusion

Child: 90 mg/kg every 6 hours (max. per dose 4.5 g)

Note: Not licensed for use in children under 12 years (except for children 2–12 years with neutropenia and complicated intra-abdominal infections).

Contraindications: Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients. History of acute severe allergic reaction to any other beta-lactam active substances (e.g., cephalosporin, monobactam or carbapenem).

Precautions: High doses may lead to hypernatraemia (owing to sodium content of preparations)

Renal Impairment: Dose adjustments:

- Child under 12 years: 78.75 mg/kg (max. 4.5 g) every 8 hours if EGFR less than 50 mL/min/1.73 m2
- Child 12–18 years: max. 4.5 g every 8 hours if EGFR 20–40 mL/min/1.73 m2, max. 4.5 g every 12 hours if EGFR less than 20 mL/min/1.73 m2
- Monitor kidney function in patients concomitantly administered with piperacillin/tazobactam and vancomycin.

Pregnancy: use only if potential benefit outweighs risk.

Breastfeeding: Trace amount in milk, but appropriate to use.

Adverse effects: Common or very common: anaemia, candida infection, constipation, GI discomfort, headache, insomnia, arthralgia, flushing, hypokalaemia, hypotension, myalgia, thrombophlebitis, epistaxis, stomatitis. Frequency not known: Eosinophilia, neutropenia, pancytopenia, pneumonia eosinophilic, renal failure, thrombocytosis

Interactions:

- Aminoglycosides: Piperacillin may inactivate aminoglycosides by converting them to microbiologically inert amides.
- Probenecid: Probenecid administered concomitantly with piperacillin and tazobactam for injection prolongs the half-life of piperacillin by 21% and that of tazobactam by 71% because probenecid inhibits tubular renal secretion of both piperacillin and tazobactam. Probenecid should not be co-administered with piperacillin and tazobactam for injection unless the benefit outweighs the risk.
- Vancomycin: Studies have detected an increased incidence of acute kidney injury in patients concomitantly administered piperacillin/tazobactam and vancomycin as compared to vancomycin alone. No pharmacokinetic interactions have been noted between piperacillin/tazobactam and vancomycin.
- Anticoagulant: Coagulation parameters should be tested more frequently and monitored regularly during simultaneous administration of high doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function.
- Neuromuscular blocking agents: Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Monitor for adverse reactions related to neuromuscular blockade.
- Methotrexate: Limited data suggests that co-administration of methotrexate and piperacillin may reduce the clearance of methotrexate due to competition for renal secretion.

Notes:

- Effect on Laboratory tests: False-positive urinary glucose (if tested for reducing substances).
- **Directions for administration:** Displacement value may be significant when reconstituting injection, consult local guidelines. For IV infusion, dilute reconstituted solution to a concentration of 15–90 mg/mL with glucose 5% or sodium chloride 0.9%, give over 30 minutes.
- **Prescribing and dispensing information:** Dose expressed as a combination of piperacillin and tazobactam (both as sodium salts) in a ratio of 8:1.

7.2.3. Reserve Group Antibiotics

These antibiotics are restricted to level 5 and 6 hospitals where they should be used under close monitoring with prescribing only done by a specialist, with guidance from the antimicrobial stewardship committee

Ceftazidime +Avibactam

ATC code: J01DD52

Powder for Injection, 2000 + 500mg, LOU 5

Indications and dose

Adult

Complicated intraabdominal infections by IV infusion: 2+0.5g every 8 hours for five to fourteen days

Complicated URTI (Upper respiratory tract infection) including pyelonephritis by IV infusion: 2+0.5g every 8 hours for five to ten days

Hospital acquired pneumonia including ventilator associated pneumonia by IV infusion: 2+0.5g every 8 hours for seven to fourteen days

Infections due gram negative bacteria with limited treatment options by IV infusion: 2+0.5g every 8 hours,

duration of treatment guided by infection severity, pathogen and Clinical and bacteriological response.

Paediatric

Complicated intraabdominal infections

Child 3–<6months: 40+10 mg/kg every 8 hours (infusion time 2 hours) for five to fourteen days

Child 6months–17 years: 50+12.5mg/kg to maximum of 2+0.5g every eight hours (infusion time two hours) for five to fourteen days

Complicated URTI (A) including pyelonephritis

Child 3–<6months: 40+10 mg/kg every 8 hours (infusion time 2 hours) for five to fourteen days

Child 6months–17 years: 50+12.5mg/kg to maximum of 2+0.5g every eight hours (infusion time two hours) for five to fourteen days

Hospital acquired pneumonia including ventilator associated pneumonia

Child 3–<6months: 40+10 mg/kg every 8 hours (infusion time 2 hours) for seven to fourteen days

Child 6months–17 years: 50+12.5mg/kg to maximum of 2/0.5g every eight hours (infusion time two hours) for seven to fourteen days

Infections due gram negative bacteria with limited treatment options

Child 3–<6months: 40+10 mg/kg every 8 hours (infusion time 2 hours) duration of treatment guided by infection severity, pathogen and Clinical and bacteriological response.

Child 6months–17 years: 50+12.5mg/kg to maximum of 2+0.5g every eight hours (infusion time two hours) duration of treatment guided by infection severity, pathogen and Clinical and bacteriological response.

Contraindications: Hypersensitivity to the Ceftazidime/Avibactam, Cephalosporins, or to any other type of β-lactam antibacterial agent (e.g. penicillin's, monobactams or carbapenems).

Precautions: Renal impairment, pediatric population at risk of overdosing.

Hepatic impairment: No dose adjustment required

Renal impairment:

Age group	Estimated CrCL (mL/min)	Dose of Ceftazidime/Avibactam	Frequency	Infusion time
Adults	31-50	1+0.25g	Every 8 hours	Every 2 hours
	16-30	0.75+0.1875g	Every 12 hours	
	6-15		Every 24 hours	
	End stage renal disease including on hemodialysis		Every 48 hours	

Age group	Estimated CrCL (mL/min)	Dose of Ceftazidime/Avibactam	Frequency	Infusion time
Paediatric patients aged 2-17 years	31-50	25+6.25mg/kg to a maximum of 1+0.25g	Every 8 hours	Every 2 hours
	16-30	18.75+4.7mg/kg to a maximum of 0.75+0.1875g	Every 12 hours	
	6-15		Every 24 hours	
	End stage renal disease including on hemodialysis		Every 48 hours	

Recommended dose for paediatric patients with CrCl less or equal to 50ml/min/1.73m2

Age group	Estimated CrCL (mL/min)	Dose of Ceftazidime/Avibactam	Frequency	Infusion time
3-<6 months	31-50	20+5mg/kg	Every 8 hours	Every 2 hours
6 months-<2years		25+6.25mg/kg	Every 8 hours	
3-<6 months	16-30	15+3.75mg/kg	Every 12 hours	
6 months-<2years		18.75+4.7mg/kg	Every 12 hours	

Note:

- There is insufficient information to recommend a dosage regimen for paediatric patients less than 2 years of age that have a CrCl <16ml/min/1.73m2

Pregnancy: use only if the potential benefit outweighs the possible risk

Breastfeeding: Ceftazidime is excreted in human milk in small quantities, It is unknown whether avibactam is excreted in human milk.

Adverse effects: Pseudomembranous colitis, Nephrotoxicity, hemolytic anemia, nausea, diarrhea, candidiasis with prolonged use, eosinophilia, thrombocytosis, headache, dizziness, abdominal pain, urticaria, pruritis, rash, pyrexia, infusion site thrombosis and phlebitis.

Interactions with other medicines: Probenecid, other nephrotoxic agents (aminoglycosides, potent diuretics like furosemide), chloramphenicol.

Notes: To be used in combination with metronidazole when anaerobic pathogens are known to be contributing to the infectious process

Colistin (Colistin Sulfomethate Sodium)

ATC code: J01XB01

Injection, 1-MU vial (as colistimethate sodium), LOU 5

Indications and doses

Adult

Serious infections due to selected aerobic Gram-negative bacteria in patients with limited treatment options by IV infusion: 9 million units daily in 2–3 divided doses; an initial loading dose of 9 million units should be used in those who are critically ill; loading and maintenance doses of up to 12 million units may be required in some cases, however, clinical experience is limited, and safety has not been established—consult product literature for details

Paediatric

Serious infections due to selected aerobic Gram-negative bacteria in patients with limited treatment options, by IV infusion

Child (body weight up to 41 kg): 75 000–150 000 units/kg daily in 3 divided doses, the data supporting the dose regimen are very limited—consult product literature for available information, including recommendation to use lean body weight for dosing

Child (body weight 41 kg and above): 9 million units daily in 2–3 divided doses, the data supporting the dose regimen are very limited—consult product literature for available information, including recommendation to use lean body weight for dosing

Contraindications: Myasthenia gravis

Precautions: Children under 1 year of age (effects of immature renal and metabolic function on conversion to active colistin not known). When used by inhalation: severe haemoptysis—risk of further haemorrhage

Hepatic impairment: With IV use manufacturer advises caution (no information available).

Renal impairment: When used by inhalation manufacturer advises caution. With IV use consult product literature.

Pregnancy: When used by inhalation: Clinical use suggests probably safe. With IV use: manufacturer advises use only if potential benefit outweighs risk.

Breastfeeding: Present in milk but poorly absorbed from gut, manufacturers advise avoid (or use only if potential benefit outweighs risk).

Adverse effects

- Common or very common, *when used by inhalation*: arthralgia, asthenia, asthma, balance impaired, chest discomfort, cough, dysphonia, dyspnoea, fever, haemorrhage, headache, lower respiratory tract infection, nausea, respiratory disorders, taste altered, throat complaints, tinnitus, vomiting
- Uncommon, *when used by inhalation:* Anxiety, appetite decreased, diarrhoea, drowsiness, ear congestion, flatulence, oral disorders, proteinuria, seizure, sputum purulent, thirst, weight change
- Rare or very rare - *with parenteral use*: confusion, nephrotoxicity, presyncope, psychosis, speech slurred and visual impairment.
- Frequency not known - *with parenteral use:* apnea, neurological effects, neurotoxicity, renal disorder and sensory disorders
- Neurotoxicity and nephrotoxicity are dose related.

Interactions:

- Concomitant use of IV colistimethate sodium with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution. Due to the effects of colistin on the release of acetylcholine, non-depolarising muscle relaxants should be used with caution in patients receiving colistimethate sodium as their effects could be prolonged.
- Co-treatment with colistimethate sodium and macrolides such as azithromycin and clarithromycin, or fluoroquinolones such as norfloxacin and ciprofloxacin should be undertaken with caution in patients with myasthenia gravis
- Concomitant use of other medicinal products with neurotoxic and/or neurotoxic potential with Colistimethate sodium should be avoided. Included are the aminoglycoside antibiotics such as amikacin, gentamycin, netilimicin and tobramycin. Concomitant use with cephalosporin antibiotics may increase risk of nephrotoxicity.

Notes:

- Colistin is best utilized in facilities with functional AMS committees. Colistin use should be guided by appropriate culture and sensitivity tests
- Colistin (Colistimethate sodium) has been used

through nebulized route in the management of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis. However, use of colistin through nebulized route is NOT approved by the US Food and Drug Administration (FDA)

» It is a polymyxin antibiotic, active against Gram-negative organisms including Pseudomonas aeruginosa, Acinetobacter baumanii, and Klebsiella pneumoniae. It is not absorbed oral and thus needs to be given by injection for a systemic effect.

» **Directions for administration:**

» When used by inhalation manufacturer advises if other treatments are being administered, they should be taken in the order recommended by the physician.

» For nebulization: consult product literature for information on reconstitution and dilution.

» For IV infusion: dilute to a concentration of 40 000 units/mL with sodium chloride 0.9%, give over 30–60 minutes. Patients fitted with a totally implantable venous access device may tolerate an injection. For slow IV injection into a totally implantable venous access device, dilute to a concentration of 90 000 units/mL with sodium chloride 0.9% for child under 12 years (200 000 units/mL for child over 12 years), give over at least 5 minutes.

» **Monitoring:**

» With IV use: Monitor renal function. In renal impairment, monitor plasma colistimethate sodium concentration during parenteral treatment—consult product literature. Recommended 'peak' plasma colistimethate sodium concentration (approx. 1 hour after IV injection or infusion) 5–15 mg/L, pre-dose ('trough') concentration 2–6 mg/L.

» When used by inhalation: Measure lung function before and after initial dose of colistimethate sodium and monitor for bronchospasm, if bronchospasm occurs in a patient not using a bronchodilator, repeat test using a bronchodilator before the dose of colistimethate sodium.

Fosfomycin

ATC code: J01XX01

Granules for oral suspension 3 g sachet, LOU 5

Powder for injection, 3-g (as sodium) vial, LOU 5

Indications and dose

Adult

Acute uncomplicated lower urinary-tract infections, oral: 3 g for 1 dose

Prophylaxis of urinary-tract infections in transurethral surgical procedures, oral: 3 g, to be given 3 hours before surgery. Dose may be repeated once, 24 hours after surgery

Osteomyelitis when first-line treatments are inappropriate or ineffective, hospital-acquired lower respiratory-tract infections when first-line treatments are inappropriate or ineffective, by IV infusion: 12–24 g daily in 2–3 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection suspected or known to be caused by less sensitive organisms

Complicated urinary-tract infections when first-line treatment ineffective or inappropriate, by IV infusion: 12–16 g daily in 2–3 divided doses (max. per dose 8 g)

Bacterial meningitis when first-line treatment ineffective or inappropriate by IV infusion: 16–24 g daily in 3–4 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection suspected or known to be caused by less sensitive organisms

Paediatric

Acute uncomplicated lower urinary-tract infections (in females), oral

Child 12–17 years (female): 3 g for 1 dose

Osteomyelitis when first-line treatments are inappropriate or ineffective, hospital-acquired lower respiratory-tract infections when first-line treatments are inappropriate or ineffective, by IV infusion

Neonate up to 40 weeks corrected gestational age: 100 mg/kg daily in 2 divided doses.

Neonate 40 weeks to 44 weeks corrected gestational age: 200 mg/kg daily in 3 divided doses.

Child 1–11 months (body weight up to 10 kg): 200–300 mg/kg daily in 3 divided doses, consider using the high-dose regimen in severe infection, particularly when suspected or known to be caused by less sensitive organisms

Child 1–11 years (body weight 10–39 kg): 200–400 mg/kg daily in 3–4 divided doses, consider using the high-dose regimen in severe infection, particularly when suspected or known to be caused by less sensitive organisms

Child 12–17 years (body weight 40 kg and above): 12–24 g daily in 2–3 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection, particularly when suspected or known to be caused by less sensitive organisms

Complicated urinary-tract infections when first-line treatment ineffective or inappropriate, by IV infusion

Neonate up to 40 weeks corrected gestational age: 100 mg/kg daily in 2 divided doses.

Neonate 40 weeks to 44 weeks corrected gestational age: 200 mg/kg daily in 3 divided doses.

Child 1–11 months (body weight up to 10 kg): 200–300 mg/kg daily in 3 divided doses, consider using the high-dose regimen in severe infection, particularly when suspected or known to be caused by less sensitive organisms

Child 1–11 years (body weight 10–39 kg): 200–400 mg/kg daily in 3–4 divided doses, consider using the high-dose regimen in severe infection, particularly when suspected or known to be caused by less sensitive organisms

Child 12–17 years (body weight 40 kg and above): 12–16 g daily in 2–3 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection, particularly when suspected or known to be caused by less sensitive organisms

Bacterial meningitis when first-line treatment ineffective or inappropriate, by IV infusion

Neonate up to 40 weeks corrected gestational age: 100 mg/kg daily in 2 divided doses.

Neonate 40 weeks to 44 weeks corrected gestational age: 200 mg/kg daily in 3 divided doses.

Child 1–11 months (body weight up to 10 kg): 200–300 mg/kg daily in 3 divided doses, consider using the high-dose regimen in severe infection, particularly when suspected or known to be caused by less sensitive organisms

Child 1–11 years (body weight 10–39 kg): 200–400 mg/kg daily in 3–4 divided doses, consider using the high dose regimen in severe infection, particularly when suspected or known to be caused by less sensitive organisms

Child 12–17 years (body weight 40 kg and above): 16–24 g daily in 3–4 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection suspected or known to be caused by less sensitive organisms

Contraindications: Hypersensitivity to the active substance or to any of the excipients

Precautions: With IV use: cardiac insufficiency, hypernatraemia, hypertension, pulmonary oedema

Renal Impairment:

- With oral use: avoid oral treatment if EGFR less than 10 mL/min/1.73 m^2.
- With IV use: age under 12 years (body weight under 40 kg)—no information available. Age 12 years and over (bodyweight over 40 kg)—use with caution if EGFR 40–80 mL/min/1.73 m^2, and consult product literature for dose if EGFR less than 40 mL/min/1.73 m^2.

Pregnancy: Manufacturer advises use only if potential benefit outweighs risk.

Breastfeeding: Manufacturer advises use only if potential benefit outweighs risk—present in milk.

Adverse effects: General Adverse effects: Common or very common: abdominal pain, diarrhoea, headache, nausea, vomiting. Uncommon: Skin reactions. Frequency not known: antibiotic associated colitis. Specific adverse effects: Common or very common: *With oral use:* Dizziness, vulvovaginal infection. *With parenteral use:* appetite decreased, dyspnoea, electrolyte imbalance, fatigue, oedema, taste altered, vertigo. Rare or very rare: *With parenteral use:* bone marrow disorders, eosinophilia, hepatic disorders, visual impairment. Frequency not known: *With parenteral use:* agranulocytosis, asthmatic attack, confusion, leucopenia, neutropenia, tachycardia, thrombocytopenia

Interactions:

- Metoclopramide reduces the serum and urinary concentrations of fosfomycin, thus avoid co-administration.
- The action of cardiac glycosides can be potentiated by hypokalemia, which may be seen with use of IV fosfomycin thus fosfomycin may decrease the excretion rate of digoxin which could result in a higher serum level.

Notes:

- Fosfomycin, a phosphonic acid antibacterial, is active against a range of Gram-positive and Gram-negative bacteria including Staphylococcus aureus, S. epidermidis, S. and Enterobacteriaceae.
- **Directions for administration:**
  - With IV use: displacement value may be significant when reconstituting injection, consult local guidelines.
  - Reconstitute each 2-g vial with 50 mL glucose 5% or glucose 10% or water for injections, do not exceed infusion rate of 133 mg/min.
  - With oral use: manufacturer advises granules should be taken on an empty stomach (about 2–3 hours before or after a meal), preferably before bedtime and after emptying the bladder. The granules should be dissolved into a glass of water and taken immediately.
- **Monitoring requirements:** With IV use Monitor electrolytes and fluid balance.

Linezolid

ATC code: J01XX08

Injection (IV),2 mg/mL in 300 mL, LOU 5

Tablet, 600 mg, LOU 5

Indications and dose

Adult

Pneumonia (when other antibacterials, e.g., a glycopetide, such as vancomycin, cannot be used) (initiated under specialist supervision with oversight from antimicrobial stewardship committee), complicated skin and soft-tissue infections caused by Gram-positive bacteria, when other antibacterials cannot be used (initiated under specialist supervision)

Oral: 600 mg every 12 hours usually for 10–14 days (maximum duration of treatment 28 days)

By IV infusion: 600 mg every 12 hours

Cellulitis (specialist use only), Erysipelas (specialist use only), Moderate diabetic foot infection (specialist use only), Severe diabetic foot infection (specialist use only), Leg ulcer infection (specialist use only), oral or by IV infusion: 600 mg every 12 hours

Paediatric

UNLICENSED USE: Not licensed for use in children

Pneumonia (when other antibacterials e.g., a glycopetide, such as vancomycin, cannot be used) (initiated under specialist supervision), Complicated skin and soft-tissue infections caused by Gram-positive bacteria, when other antibacterials cannot be used (initiated under specialist supervision)

Oral or by IV infusion

Neonate up to 7 days: 10 mg/kg every 12 hours, increased if necessary to 10 mg/kg every 8 hours, increased dose can be used if poor response

Neonate 7 days to 28 days: 10 mg/kg every 8 hours

Child 1 month–11 years: 10 mg/kg every 8 hours (max. per dose 600 mg)

Child 12–17 years: 600 mg every 12 hours

Cellulitis (specialist use only), erysipelas (specialist use only), oral, or by IV infusion

Child 1 month–11 years: 10 mg/kg every 8 hours (max. per dose 600 mg)

Child 12–17 years: 600 mg every 12 hours

Contraindications: Hypersensitivity to linezolid or to any of the excipients. Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g., phenelzine, isocarboxazid, selegiline, moclobemide) or within two weeks of taking any such medicinal product.

Precautions: Acute confusional states, bipolar depression, carcinoid tumour, history of seizures, phaeochromocytoma, schizophrenia, thyrotoxicosis, uncontrolled hypertension: Unless close observation and blood pressure monitoring possible, linezolid should be avoided in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia, or acute confusional states.

IMPORTANT SAFETY INFORMATION

Optic neuropathy: Severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days.

- Patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and colour vision) immediately
- Patients experiencing new visual symptoms (regardless of treatment duration) should be evaluated promptly, and referred to an ophthalmologist if necessary.
- Visual function should be monitored regularly if treatment is required for longer than 28 days.

Blood disorders: Haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) have been reported in patients receiving linezolid. It is recommended that full blood counts are monitored weekly. Close monitoring is recommended in patients who:

- Receive treatment for more than 10–14 days
- Have pre-existing myelosuppression
- Are receiving drugs that may have adverse effects on haemoglobin, blood counts, or platelet function
- Have severe renal impairment

If significant myelosuppression occurs, treatment should be stopped unless it is considered essential, in which case intensive monitoring of blood counts and appropriate management should be implemented.

Hepatic Impairment: Manufacturer advises caution in severe impairment (no information available).

Renal Impairment: Manufacturer advises metabolites may accumulate if eGFR less than 30 mL/min/1.73 m2.

Pregnancy: Manufacturer advises use only if potential benefit outweighs risk—no information available.

Breastfeeding: Manufacturer advises avoid—present in milk in animal studies.

Adverse effects: Common or very common: Anaemia, constipation, diarrhoea, dizziness, GI discomfort, headache, hypertension, increased risk of infection, insomnia, localised pain, nausea, skin reactions, taste altered, vomiting. Uncommon: Arrhythmia, chills, dry mouth, eosinophilia, fatigue, gastritis, hyperhidrosis, hyponatraemia, leucopenia, neutropenia, oral disorders, pancreatitis, polyuria, renal failure, seizure, sensation abnormal, thirst, thrombocytopenia, thrombophlebitis, tinnitus, tongue discolouration, transient ischaemic attack, vision disorders, vulvovaginal disorder. Rare or very rare: Antibiotic associated colitis, bone marrow disorders, tooth discolouration. Frequency not known: Alopecia, angioedema, lactic acidosis, nerve disorders, serotonin syndrome, SCARs

Interactions

- Serotonin syndrome: Spontaneous reports of serotonin syndrome including fatal cases associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported.
- Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g., pseudoephedrine), vasopressive agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine)

Notes:

- Linezolid, an oxazolidinone antibacterial, is active against Gram-positive bacteria including MRSA, and glycopeptide resistant enterococci. Resistance to linezolid can develop with prolonged treatment or if the dose is less than that recommended. Linezolid is not active against common Gram-negative organisms; it must be given in combination with other antibacterials for mixed infections that also involve Gram-negative organisms.
- Monitoring requirements: Monitor full blood count (including platelet count) weekly.
- **Directions for administration:** With IV use infusion to be administered over 30–120 minutes.

Meropenem

ATC code: J01DH02

Powder for injection, 500 mg as trihydrate, LOU 5

Indications and dose

Adult

Aerobic and anaerobic Gram-positive and Gram-negative infections, hospital-acquired sepsis, by IV infusion or IV injection: 0.5–1 g every 8 hours

Exacerbations of chronic lower respiratory-tract infection in cystic fibrosis, by IV infusion or IV injection: 2 g every 8 hours

Meningitis, by IV infusion or IV injection: 2 g every 8 hours

Endocarditis (in combination with another antibacterial), by IV infusion or IV injection: 2 g every 8 hours

Paediatric

UNLICENSED USE: Not licensed for use in children under 3 months.

Aerobic and anaerobic Gram-positive and Gram-negative infections, hospital-acquired septicaemia, by IV infusion or IV injection

Neonate up to 7 days: 20 mg/kg every 12 hours.

Neonate 7 days to 28 days: 20 mg/kg every 8 hours.

Child 1 month–11 years (body weight up to 50 kg): 10–20 mg/kg every 8 hours

Child 1 month–11 years (body weight 50 kg and above): 0.5–1 g every 8 hours

Child 12–17 years: 0.5–1 g every 8 hours

Severe aerobic and anaerobic Gram-positive and Gram-negative infections, by IV infusion, or by IV injection

Neonate up to 7 days: 40 mg/kg every 12 hours.

Neonate 7 days to 28 days: 40 mg/kg every 8 hours.

Exacerbations of chronic lower respiratory-tract infection in cystic fibrosis by IV infusion

Child 1 month–11 years (body weight up to 50 kg): 40 mg/kg every 8 hours

Child 1 month–11 years (body weight 50 kg and above): 2 g every 8 hours

Child 12–17 years: 2 g every 8 hours

Meningitis by IV infusion

Neonate up to 7 days: 40 mg/kg every 12 hours

Neonate 7 days to 28 days: 40 mg/kg every 8 hours

Child 1 month–11 years (body weight up to 50 kg): 40 mg/kg every 8 hours

Child 1 month–11 years (body weight 50 kg and above): 2 g every 8 hours

Child 12–17 years: 2 g every 8 hours

Precautions: Allergy and cross sensitivity: Avoid if history of immediate hypersensitivity reaction to beta-lactam antibacterials. Use with caution in patients with sensitivity to beta-lactam antibacterials.

Renal Impairment: Dose adjustments:

- Use normal dose every 12 hours if EGFR 26–50 mL/min/1.73 m².
- Use half normal dose every 12 hours if EGFR 10–25 mL/min/1.73 m².
- Use half normal dose every 24 hours if EGFR less than 10 mL/min/1.73 m².

Pregnancy: Use only if potential benefit outweighs risk— no information available.

Breastfeeding: Unlikely to be absorbed (however, manufacturer advises avoid).

Adverse effects: Common or very common: Abdominal pain, diarrhoea, headache, inflammation, nausea, pain, skin reactions, thrombocytosis, vomiting. Uncommon: Agranulocytosis, antibiotic associated colitis, eosinophilia, haemolytic anaemia, increased risk of infection, leucopenia, neutropenia, paraesthesia, SCARs, thrombocytopenia,

Thrombophlebitis. Rare: Seizure.

Interactions:

- Probenecid: Concomitant administration of meropenem and probenecid results in increases in the plasma level and half-life of meropenem. Therefore, it is not recommended that probenecid be given concomitantly with meropenem.
- Valproic acid: decreased valproic acid plasma concentrations and loss of anticonvulsant effect.

Notes:

- Dosing, efficacy and safety in children under 3 months is indeterminate, dose with caution and monitoring
- Monitoring Requirements: Manufacturer advises monitor liver function—risk of hepatotoxicity.
- **Directions for administration:** IV infusion to be given over 15–30 minutes, bolus to be given over 5 minutes. Bolus should be given to a maximum of 1 g. For IV infusion, dilute reconstituted solution further to a concentration of 1–20 mg/mL in glucose 5% or sodium chloride 0.9%, give over 15–30 minutes. Displacement value may be significant when reconstituting injection, consult local guidelines.
- Effect on laboratory tests: Positive Coombs' test

Polymyxin B

ATC code: J01XB02

Powder for injection, 500,000-IU vial, LOU 5

Indications and dose:

Acute infections caused by susceptible strains of Pseudomonas aeruginosa.

Polymyxin B sulphate is a drug of choice in the treatment of infections of the urinary tract, meninges, and bloodstream caused by susceptible strains of Ps.

aeruginosa. It may be indicated in serious infections caused by susceptible strains of the following organisms, when less potentially toxic drugs are ineffective or contraindicated:

H influenzae, specifically meningeal infections.

Escherichia coli, specifically urinary tract infections.

Aerobacter aerogenes, specifically bacteremia.

Klebsiella pneumoniae, specifically bacteremia.

Adult

By IV:

15,000 to 25,000 units/kg body weight/day in individuals with normal kidney function. This amount should be reduced from 15,000 units/kg downward for individuals with kidney impairment. Infusions may be given every 12 hours, however, the total daily dose must not exceed 25,000 units/kg/day.

Dissolve 500,000 polymyxin B units in 300 to 500 mL solutions for parenteral 5% dextrose injection for continuous drip.

By IM (not recommended routinely because of severe pain at injection sites, particularly in infants and children).

25,000 to 30,000 units/kg/day. This should be reduced in the presence of renal impairment. The dosage may be divided and given at either 4- or 6-hour intervals.

Dissolve 500,000 polymyxin B units in 2 mL sterile water for injection or 0.9% sodium chloride injection or procaine HCl injection 1%.

Ps aeruginosa meningitis, Intrathecal

50,000 units once daily intrathecally for 3 to 4 days, then 50,000 units once every other day for at least 2 weeks after cultures of the cerebrospinal fluid are negative and sugar content has returned to normal.

Dissolve 500,000 polymyxin B units in 10 mL 0.9% sodium chloride injection USP for 50,000 units per mL dosage unit.

Paediatric

Acute infections caused by susceptible strains of Pseudomonas aeruginosa.

Polymyxin B sulphate is a drug of choice in the treatment of infections of the urinary tract, meninges, and bloodstream caused by susceptible strains of Ps. aeruginosa. It may be indicated in serious infections caused by susceptible strains of the following organisms, when less potentially toxic drugs are ineffective or contraindicated:

H influenzae, specifically meningeal infections.

Escherichia coli, specifically urinary tract infections.

Aerobacter aerogenes, specifically bacteremia.

Klebsiella pneumoniae, specifically bacteremia.

By IV

Infant: Infants with normal kidney function may receive up to 40,000 units/kg/day without adverse effects.

Child: 15,000 to 25,000 units/kg body weight/day in individuals with normal kidney function. This amount should be reduced from 15,000 units/kg downward for individuals with kidney impairment. Infusions may be given every 12 hours, however, the total daily dose must not exceed 25,000 units/kg/day.

Dissolve 500,000 polymyxin B units in 300 to 500 mL solutions for parenteral 5% dextrose injection for continuous drip.

By IM

Not recommended routinely because of severe pain at injection sites, particularly in infants and children.

Infant: with normal kidney function may receive up to 40,000 units/kg/day without adverse effects.

Child: 25,000 to 30,000 units/kg/day. This should be reduced in the presence of renal impairment. The dosage may be divided and given at either 4 or 6 hour intervals.

Dissolve 500,000 polymyxin B units in 2 mL sterile water for injection or 0.9% sodium chloride injection or procaine HCl injection 1%.

Note: Doses as high as 45,000 units/kg/day have been used in limited clinical studies in treating prematures and newborn infants for sepsis caused by Ps aeruginosa.

Ps aeruginosa meningitis, Intrathecal

Child over 2years: 50,000 units once daily intrathecally for 3 to 4 days, then 50,000 units once every other day for at least 2 weeks after cultures of the cerebrospinal fluid are negative and sugar content has returned to normal.

Child under 2 years: 20,000 units once daily, intrathecally for 3 to 4 days or 25,000 units once every other day. Continue with a dose of 25,000 units once every other day for at least 2 weeks after cultures of the cerebrospinal fluid are negative and sugar content has returned to normal.

Dissolve 500,000 polymyxin B units in 10 mL 0.9% sodium chloride injection USP for 50,000 units per mL dosage unit.

Contraindications: This drug is contraindicated in persons with a prior history of hypersensitivity reactions to polymyxins.

Warning: CDAD has been reported with use of nearly all antibacterial agents, including Polymyxin B for injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to

occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Precautions:

- General. Prescribing polymyxin B in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- When this drug is given intramuscularly and/or intrathecally, it should be given only to hospitalized patients, to provide constant supervision by a physician.
- Renal function should be carefully determined and patients with renal damage and nitrogen retention should have reduced dosage. Patients with nephrotoxicity due to polymyxin b sulphate usually show albuminuria, cellular casts, and azotemia. Diminishing urine output and a rising bun are indications for discontinuing therapy with this drug.
- Neurotoxic reactions may be manifested by irritability, weakness, drowsiness, ataxia, perioral paresthesia, numbness of the extremities, and blurring of vision. These are usually associated with high serum levels found in patients with impaired renal function and/or nephrotoxicity.
- The concurrent or sequential use of other neurotoxic and/or nephrotoxic drugs with polymyxin b sulphate, particularly bacitracin, streptomycin, neomycin, kanamycin, gentamicin, tobramycin, amikacin, cephaloridine, paromomycin, viomycin, and colistin should be avoided.
- The neurotoxicity of polymyxin b sulphate can result in respiratory paralysis from neuromuscular blockade, especially when the drug is given soon after anesthesia and/or muscle relaxants.
- Usage in pregnancy: the safety of this drug in human pregnancy has not been established.

Interactions:

- Avoid concurrent use of a curariform muscle relaxant and other neurotoxic drugs (ether, tubocurarine, succinylcholine, gallamine, decamethonium and sodium citrate) which may precipitate respiratory depression. If signs of respiratory paralysis appear, respiration should be assisted as required, and the drug discontinued.
- Nephrotoxic reactions: Albuminuria, cylinduria, azotemia, and rising blood levels without any increase in dosage.
- Neurotoxic reactions: Facial flushing, dizziness progressing to ataxia, drowsiness, peripheral paresthesias (circumoral and stocking glove), apnea due to concurrent use of curariform muscle relaxants, other neurotoxic drugs or inadvertent overdosage, and signs of meningeal irritation with intrathecal administration, e.g., fever, headache, stiff neck and increased cell count and protein cerebrospinal fluid.
- Other reactions occasionally reported: Drug fever, urticarial rash, pain (severe) at IM injection sites, and thrombophlebitis at IV injection sites.

Note:

- In meningeal infections, polymyxin b sulphate should be administered only by the intrathecal route.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of polymyxin B and other antibacterial drugs, polymyxin B should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology
- In the interest of safety, solutions of parenteral use should be stored under refrigeration, and any unused portions should be discarded after 72 hours.
- Baseline renal function should be done prior to therapy, with frequent monitoring of renal function and blood levels of the drug during parenteral therapy.

Teicoplanin

ATC code: J01XA02

Injection, 200 mg, LOU 5

Indications and doses

Adult

Moderate diabetic foot infection, severe diabetic foot, infection, leg ulcer infection by IV injection, or by IV infusion: Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily

Cellulitis, erysipelas, by IV injection, or by IV infusion: Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily

Serious infections caused by Gram-positive bacteria (e.g., complicated skin and soft-tissue infections, pneumonia, complicated urinary tract infections) by IV injection or IV infusion or IM injection: Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily

Streptococcal or enterococcal endocarditis (in combination with another antibacterial), bone and joint infections by IV injection or by IV infusion: 12 mg/kg every 12 hours for 3–5 doses, then (by IV injection or IV infusion or IM injection) 12 mg/kg once daily; duration of treatment is usually a minimum of 21 days but should not exceed 4 months.

Surgical prophylaxis by IV injection: 400 mg, to be

administered up to 30 minutes before the procedure

Surgical prophylaxis in open fractures by IV infusion: 800 mg, to be administered up to 30 minutes before skeletal stabilisation and definitive soft-tissue closure

Peritonitis associated with peritoneal dialysis (added to dialysis fluid), by intraperitoneal infusion: Consult local protocol

Paediatric

Cellulitis, erysipelas, by IV injection or IV infusion

Child 1 month: Initially 16 mg/kg for 1 dose, followed by 8 mg/kg once daily, subsequent dose to be administered 24 hours after initial dose, doses to be given by IV infusion

Child 2 months–11 years: Initially 10 mg/kg every 12 hours for 3 doses, then 6–10 mg/kg once daily

Child 12–17 years: Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily

Serious infections caused by Gram-positive bacteria (e.g., complicated skin and soft-tissue infections, pneumonia, complicated urinary tract infections) by IV injection or IV infusion or IM injection

Child 12–17 years: Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily

Streptococcal or enterococcal endocarditis (in combination with another antibacterial), bone and joint infections, initially by IV injection or IV infusion

Child 12–17 years: 12 mg/kg every 12 hours for 3–5 doses, then (by IV injection or IV infusion or IM injection) 12 mg/kg once daily; duration of treatment is no less than 3 weeks and no more than 4 months

Surgical prophylaxis, by IV injection

Child: Consult local protocol

Serious infections caused by Gram-positive bacteria (including endocarditis, complicated skin and soft-tissue infections, pneumonia, complicated urinary tract infections, bone and joint infections), by IV injection or IV infusion

Neonate: Initially 16 mg/kg for 1 dose, followed by 8 mg/kg once daily, subsequent dose to be administered 24 hours after initial dose, doses to be given by IV infusion.

Child 1 month: Initially 16 mg/kg for 1 dose, followed by 8 mg/kg once daily, subsequent dose to be administered 24 hours after initial dose, doses to be given by IV infusion

Child 2 months–11 years: Initially 10 mg/kg every 12 hours for 3 doses, then 6–10 mg/kg once daily

Peritonitis-associated with peritoneal dialysis (added to dialysis fluid), by intraperitoenal infusion

Child 12–17 years: Consult local protocol

Precautions

Renal impairment: Use normal dose regimen on days 1–4, then use normal maintenance dose every 48 hours if EGFR 30–80 mL/min/1.73 m2 and use normal maintenance dose every 72 hours if EGFR less than 30 mL/min/1.73 m2.

Monitor renal and auditory function during prolonged treatment in renal impairment.

Pregnancy: use only if potential benefit outweighs risk.

Breastfeeding: No information available.

Adverse effects: Common or very common: Fever pain, skin reactions, Uncommon: Bronchospasm, diarrhoea, dizziness, eosinophilia, headache, hearing impairment, hypersensitivity, leucopenia, nausea, ototoxicity, thrombocytopenia, vomiting. Rare or very rare: Abscess, red man syndrome. Frequency not known: Agranulocytosis, angioedema, chills, neutropenia, overgrowth of nonsusceptible organisms, renal impairment, seizure, SCARs, thrombophlebitis

Interactions:

Teicoplanin and aminoglycoside solutions are incompatible and must not be mixed for injection, however, they are compatible in dialysis fluid and may be freely used in the treatment of CAPD-related peritonitis.

Teicoplanin should be used with care in conjunction with or sequentially with other medicinal products with known nephrotoxic or ototoxic potential. These include aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide, and ethacrynic acid.

Notes:

- Teicoplanin is similar to vancomycin, but has a significantly longer duration of action, allowing once daily administration after the loading dose.
- Teicoplanin is associated with a lower incidence of nephrotoxicity than vancomycin.
- Allergy and cross-sensitivity: Caution if history of vancomycin sensitivity.
- Unless treating a single susceptible organism, preferable to use combination therapy as it mostly covers Gram positive organisms.
- Monitoring requirements:
- With IM use or IV use manufacturer advises monitor serum-teicoplanin trough concentration at steady state after completion of loading dose and during maintenance treatment—product literature recommends the following trough levels: At least 10 mg/L, 15 mg/L for most susceptible infections, 20 mg/L for Bone and Joint infections, 30 mg/L for Infective endocarditis. Trough concentrations should be monitored weekly.
- Blood counts and liver and kidney function tests required.
- Manufacturer advises monitoring for adverse reactions when doses of 12 mg/kg twice daily are administered.
- IV use directions for administration: For intermittent IV infusion, dilute reconstituted solution further in sodium chloride 0.9% or glucose 5%, give over 30 minutes.
- Bolus dose should be given over 3–5 minutes,

but do not give bolus in neonates.

With oral use injection can be used to prepare solution for oral administration.

- PHARMACOKINETICS: Teicoplanin should not be given oral for systemic infections because it is not absorbed significantly, only give for *C. difficile*.
- UNLICENSED USE Not licensed for surgical prophylaxis

Tigecycline

ATC code: J01AA12

Powder for injection, 50-mg vial, LOU 5

Indications and dose

Adult

Complicated skin and soft tissue infections (when other antibiotics are not suitable), Complicated intraabdominal infections (when other antibiotics are not suitable), by *IV infusion:* Initially 100 mg, followed by 50 mg every 12 hours for 5–14 days

Paediatric: Not for use in children/adolescents <18 years as its safety and efficacy is not established

Contraindications: Children under 8 years (deposition in growing bone and teeth, by binding to calcium, causes staining and occasionally dental hypoplasia), diabetic foot infections. Allergy and cross-sensitivity: Contraindicated in patients hypersensitive to tetracyclines.

Precautions: Cholestasis

Hepatic impairment: Manufacturer advises caution in severe impairment.

Dose adjustments Manufacturer advises dose reduction of 50% in severe impairment.

development have been documented in the first trimester in animal studies.

Pregnancy: Tetracyclines should not be given to pregnant women, effects on skeletal

Note: Administration during the second or third trimester may cause discoloration of the child's teeth, and maternal hepatotoxicity has been reported with large parenteral doses.

Breastfeeding: Manufacturer advises avoid—present in milk in animal studies.

Adverse effects: Common or very common: Abscess, appetite decreased, diarrhoea, dizziness, GI discomfort, headache, healing impaired, hyperbilirubinaemia, elevated ALT/AST, hypoglycaemia, hypoproteinaemia, increased risk of infection, nausea, sepsis, skin reactions, vomiting, phlebitis, prolonged APTT and prolonged PT. Uncommon: Hepatic disorders, pancreatitis, thrombocytopenia, thrombophlebitis. Frequency not known: Acidosis, azotaemia, hyperphosphataemia, hypofibrinogenaemia, idiopathic intracranial hypertension, photosensitivity reaction, pseudomembranous enterocolitis, SCARs, tooth discolouration. **Note**: Adverse effects similar to those of the tetracyclines can potentially occur.

Interactions:

Tigecycline increases the risk of bleeding events when given with coumarins.

Notes:

- Tigecycline is a glycylcycline antibacterial structurally related to the tetracyclines. Tigecycline is active against Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobes. It is also active against MRSA and vancomycin-resistant enterococci, but pseudomonas aeruginosa and many strains of Proteus spp. are resistant to tigecycline.
- DIRECTIONS FOR ADMINISTRATION: For IV infusion, give intermittently in glucose 5% or sodium chloride 0.9%. Reconstitute each vial with 5.3 mL infusion fluid to produce a 10 mg/mL solution, dilute requisite dose in 100 mL infusion fluid, give over 30–60 minutes (preferably 60 minutes in paediatrics).
- Manufacturer advises monitor liver function tests, amylase, lipase, coagulation and haematology parameters before starting treatment, and regularly during treatment.
- Driving and skilled tasks: Manufacturer advises patients and Caregivers should be cautioned on the effects on driving and performance of skilled tasks—increased risk of dizziness.

Vancomycin

ATC code: J01XA01

Powder for injection, 500 mg (as HCl) in vial, LOU 5

Indications and dosage

Treatment of infections with susceptible organisms, including methicillin-resistant staphylococcal pneumonia, staphylococcal meningitis, antibiotic-associated colitis, endocarditis treatment and prophylaxis; local antimicrobial patterns need to be taken into account.

Adult

Serious staphylococcal infections, by IV infusion: 500 mg over at least 60 minutes every 6 hours or 1 g over at least 100 minutes every 12 hours

Elderly (over 65 years): 500 mg every 12 hours or 1 g once daily

Antibiotic-associated colitis, oral: **ADULT,** 125–500 mg every 6 hours for 7–10 days

Endocarditis prophylaxis (for procedures under general anaesthetic), by IV infusion: 1 g over at least 100 minutes, then gentamicin 120 mg at induction or 15 minutes before procedure

Paediatric

Serious staphylococcal infections, by IV infusion

Neonate up to 1 week: 15 mg/kg initially, then 10 mg/kg every 12 hours

Neonate 1–4 weeks: 15 mg/kg initially, then 10 mg/kg every 8 hours

Child over 1 month: 10 mg/kg every 6 hours

Antibiotic-associated colitis, oral

Child 1 month–5 years: 5 mg/kg every 6 hours

Child over 5 years: 62.5 mg every 6 hours

Contraindications: History of deafness.

Precautions: Avoid rapid infusion (risk of anaphylactoid reactions, see Adverse effects), rotate infusion sites, renal impairment, monitor plasma vancomycin concentration (after three or four doses in normal renal function, earlier if renal impairment), blood counts, urine analysis and renal function tests: use only in hospital setting, monitor auditory function and plasma vancomycin concentrations in renal impairment.

Therapeutic drug monitoring: Plasma concentration monitoring required, pre-dose (trough) concentration should be 10–15 mg/L (15–20 mg/L for less sensitive strains of methicillin-resistant

Renal impairment: Increase dose interval or reduce dose, or both, in renal impairment. Monitor plasma vancomycin concentration and renal function regularly.

Adverse effects: Common IV: local pain (may be severe), thrombophlebitis. Oral: usually only causes GI adverse effects if significant serum concentrations occur, e.g., in renal impairment.

Nausea, vomiting, diarrhoea and chills.

Nephrotoxicity including renal failure (see below).

Rare Ototoxicity (discontinue if tinnitus occurs), interstitial nephritis, serious skin reactions (e.g., linear IgA bullous disease, exfoliative dermatitis, erythema multiforme (SJS), toxic epidermal necrolysis, vasculitis, drug rash with eosinophilia and systemic symptoms). Blood disorders including thrombocytopenia (may be immune-mediated), neutropenia (more likely after at least 1 week and total dose > 25 g), leukopenia, agranulocytosis, flushing of the upper body ("red man" syndrome [see below]), anaphylaxis, severe hypotension (with shock, cardiac arrest), superinfection, CDAD.

Nephrotoxicity: Although reports of frequency are conflicting, it is more common when used with aminoglycosides and in renal impairment. It appears to be related to vancomycin serum concentration.

Ototoxicity Dizziness, vertigo and tinnitus can occur. Vancomycin alone rarely causes ototoxicity, risk is higher with prolonged use, in renal impairment and when given with other ototoxic drugs, e.g., aminoglycosides, deafness may be permanent.

Red man syndrome usually due to infusion being given too quickly. It is not an allergic reaction although symptoms are partly due to histamine release, they include fever, chills, erythema, facial and upper torso rash, which may be followed by hypotension, angioedema and itch. May be treated with antihistamines (e.g., promethazine), successful administration is usually possible by increasing the infusion time (e.g., to 120 minutes).

Interactions (*indicates serious):

- Amikacin: increased risk of nephrotoxicity and ototoxicity.
- Amphotericin B: possibly increased risk of nephrotoxicity.
- Capreomycin: increased risk of nephrotoxicity and ototoxicity.
- * Ciclosporin: increased risk of nephrotoxicity.
- * Furosemide: increased risk of ototoxicity.
- Gentamicin: increased risk of nephrotoxicity and ototoxicity.
- Halothane: hypersensitivity-like reactions can occur with concomitant IV vancomycin.
- Ketamine: hypersensitivity-like reactions can occur with concomitant IV vancomycin.
- Nitrous oxide: hypersensitivity-like reactions can occur with concomitant IV vancomycin.
- Paromomycin: increased risk of otoxicity.
- Streptomycin: increased risk of nephrotoxicity and ototoxicity.
- * Suxamethonium: enhanced effects of suxamethonium.
- Thiopental: hypersensitivity-like reactions can occur with concomitant IV vancomycin.

Notes:

- Vancomycin is a complementary antibacterial drug for use only when there is significant resistance to other drugs on the WHO Model List of Essential Medicines for Children.
- Duration of treatment is 7–14 days for non-necrotizing infections, colitis, community and nosocomial pneumonia, for Necrotizing skin infections and bone and joint infections as well as Infective endocarditis duration is 4–6 weeks.
- Injection may be given orally for *C. difficile* infection (see Dose), injection can be used to prepare a solution for oral administration. Flavouring syrups may be added to the solution at the time of administration.
- Administration Give over at least 60 minutes (rate not to exceed 10 mg/min for doses > 500 mg) via CVC, if possible, this is to avoid infusion reactions, avoid extravasation, never give IM. Do not mix with other drugs in parenteral solutions.

7.2.4. Antileprosy Medicines

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance.

Clofazimine

ATC code: J04BA01

Capsule, 50 mg, 100 mg, LOU 4

Indications and dose

Treatment of multibacillary (MB) leprosy (and where classification between MB and paucibacillary leprosy cannot be made) as part of combination therapy, treatment of type 2 lepra reactions (erythema nodosum leprosum).

Adult

Multibacillary leprosy (in combination with dapsone and rifampicin, see also introductory note above), oral: 50 mg once daily and 300 mg once a month

Type 2 lepra reaction (erythema nodosum leprosum), oral:

100–200 mg daily in 2 or 3 divided doses for a maximum of 3 months, 4–6 weeks treatment may be required before any effect is seen; gradually taper the dose to 100 mg daily as soon as possible after the reactive episode is controlled; given in combination with baseline antileprosy treatment and corticosteroids (as clinically indicated)

Paediatric

Multibacillary leprosy (in combination with dapsone and rifampicin), oral

Child under 10 years: 100 mg once a month and 50 mg twice a week; continue treatment for 12 months

Child 10–12 years: 150 mg once a month and 50 mg on alternate days; continue treatment for 12 months

Type 2 lepra reaction (erythema nodosum leprosum), oral

Child all ages: 100 mg two or three times daily; continue treatment for 3 months; 4–6 weeks treatment may be required before effect is seen

Precautions: Pre-existing GI symptoms (reduce dose, increase dose interval or discontinue if symptoms develop during treatment), liver and renal impairment, may discolour soft contact lenses, patients with risk factors for QT prolongation, history of depression, hepatic and severe renal impairment, pregnancy and breastfeeding.

Skilled tasks: Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for about 24 hours.

Adverse effects: Reversible discoloration of skin, hair, cornea, conjunctiva, tears, sweat, sputum, faeces and urine, GI pain, nausea, vomiting, diarrhoea, weight loss, GI bleeding, severe mucosal and submucosal oedema, dry skin, acne-like eruptions, rashes, pruritus, photosensitivity, decreased sweat production, dry eyes. Rare: Headache, drowsiness, dizziness, taste disorders, elevation of blood glucose concentration. **Potentially Fatal:** Splenic infarction, GI bleeding.

Interactions with other medicines (*indicates serious):

- *Phenytoin: reduced phenytoin serum concentrations and loss of phenytoin efficacy.
- Increased risk of additive torsades de pointes and QT prolongation with other agents known to prolong QT interval (e.g., bedaquiline).
- May increase the serum concentrations of CYP3A4/5 substrates.

Notes: The drug is well tolerated and virtually non-toxic in the dosage used for multidrug therapy. The drug causes brownish black discoloration and dryness of skin. However, this disappears within a few months after stopping treatment. This should be explained to patients starting a multidrug therapy regimen for multibacillary leprosy.

Dapsone

ATC code: J04BA02

Tablet, 100 mg, 25 mg, LOU 4

Indications and dose

Treatment of leprosy as part of combination therapy (paucibacillary and multibacillary)

Adult

Paucibacillary leprosy (in combination with rifampicin), oral: 100 mg daily for at least 6 months

Multibacillary leprosy (in combination with rifampicin and clofazimine), oral: 100 mg daily continue treatment for 12 months

Paediatric

Paucibacillary leprosy (in combination with rifampicin), oral

Child under 10 years: 25 mg once daily; continue treatment for 6 months

Chile 10–12 years: 50 mg once daily; continue treatment for 6 months

Multibacillary leprosy (in combination with rifampicin and clofazimine), oral

Child under 10 years: 25 mg once daily; continue treatment for 12 months

Child 10–12 years: 50 mg once daily; continue treatment for 12 months

Contraindications: Hypersensitivity to sulfones, severe anaemia, porphyria, severe G6PD deficiency.

Precautions: Anaemia (treat severe anaemia before therapy, and monitor blood counts during treatment), susceptibility to haemolysis including G6PD deficiency (including breastfeeding affected infants), porphyria. Patient with history of hypersensitivity to sulfonamides, cardiac disease, pulmonary disease, diabetes mellitus, methaemoglobin reductase deficiency, moderate hepatic impairment, children, pregnancy and breastfeeding. Blood disorders: On long-term treatment, patients and their Caregivers should be told how to recognize blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. **Skilled tasks**: Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Renal impairment: Increased levels can occur in renal impairment.

Adverse effects: Common: GI irritation, photosensitivity. Rare: Haemolysis, methaemoglobinaemia, allergic dermatitis (rarely including toxic epidermal necrolysis and SJS), hepatitis, agranulocytosis, "dapsone syndrome" resembling mononucleosis (rare hypersensitivity reaction with symptoms including rash, fever, jaundice, and eosinophilia), tachycardia, headache, nervousness, insomnia, blurred vision, paraesthesia, reversible peripheral neuropathy, psychoses.

Interactions with other medicines (*indicates serious):

- Rifampicin: reduced plasma dapsone concentration.
- Sulfamethoxazole + trimethoprim: plasma

concentration of both dapsone and trimethoprim may increase with concomitant use.

» Plasma concentrations may be increased by probenecid. May reduce the efficacy of oral typhoid vaccine

» May increase the risk of arrhythmia with saquinavir.

Notes:

» May cause photosensitivity.

» Patients with high acetylation rates or who are receiving treatment that affects acetylation may require a dosage adjustment.

» May be taken with food to reduce stomach upset.

» Tablets should be taken whole and small doses should be made up from 25 mg tablets. Do not split the tablet.

Rifampicin

ATC code: J04AB02

Tablet/capsule, 150 mg, 300 mg, LOU 4

Indications and dose

Treatment of leprosy as part of combination therapy (paucibacillary and multibacillary).

Adult

Paucibacillary leprosy (in combination with dapsone, see also introductory note above), oral: 600 mg once a month. Alternatively, 10 mg/kg once monthly. Max: 450 mg for patients weighing <50 kg, 600 mg for patients weighing ≥50 kg.

Multibacillary leprosy (in combination with dapsone and clofazimine, see note above), oral: 600 mg once a month under supervision, continue treatment for 12 months.

Paediatric

Paucibacillary leprosy (in combination with dapsone), oral

Child under 10 years: 300 mg once a month; continue treatment for 6 months

Child 10–12 years: 450 mg once a month; continue treatment for 6 months

Multibacillary leprosy (in combination with dapsone and clofazimine), oral

Child under 10 years: 300 mg once a month. Continue treatment for 12 months

Child 10–12 years: 450 mg once a month; continue treatment for 12 months

Contraindications: Hypersensitivity to rifamycins, jaundice, concomitant use with saquinavir/ritonavir combination, atazanavir, darunavir, fosamprenavir, saquinavir, tipranavir.

Precautions: Hepatic impairment, monitor liver function tests and blood counts in patients with liver disorders or on prolonged therapy, renal impairment (if dose above 600 mg daily), porphyria, discolours soft contact lenses. Patient with current or history of alcoholism, risk factors of vitamin K deficiency (e.g., chronic liver disease, poor nutritional status, receiving prolonged antibacterial or anticoagulant therapy), diabetes mellitus, children and elderly, pregnancy, and breastfeeding.

Important: Advise patients on hormonal contraceptives to use additional means.

Note: Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, haemolysis or thrombocytopenia, discontinue permanently if serious adverse effects occur.

Liver disorders: Patients or their Caregivers should be told how to recognize signs of liver disorders and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise, or jaundice develop.

Hepatic impairment: Impaired elimination, monitor liver function, avoid or do not exceed 8 mg/kg daily.

Adverse effects: Common: Urine, tears, saliva and sputum coloured orange-red. Rare: Alterations of liver function, jaundice, potentially fatal hepatitis (dose related, do not exceed maximum dose of 600 mg daily), anorexia, nausea, vomiting, diarrhoea, antibiotic-associated colitis, headache, drowsiness, rashes, fever, influenza-like syndrome, respiratory symptoms, collapse, shock, haemolytic anaemia, acute renal failure, thrombocytopenic purpura, oedema, muscular weakness, myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia, menstrual disturbances. Frequency not known: Vitamin K-dependent coagulopathy, bleeding. Facial or peripheral oedema.

Interactions with other medicines (*indicates serious):

Abacavir: plasma concentration of abacavir possibly reduced.

Amitriptyline: plasma concentration of amitriptyline possibly reduced.

Antacids (aluminium hydroxide, magnesium hydroxide): reduced absorption of rifampicin.

Chloramphenicol: accelerated metabolism of chloramphenicol (reduced plasma chloramphenicol concentration).

* Ciclosporin: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).

* Contraceptives, oral: accelerated metabolism of estrogens and progestogens (reduced contraceptive effect).

Dapsone: reduced plasma dapsone concentration.

* Dexamethasone: accelerated metabolism of dexamethasone (reduced effect).

Diazepam: metabolism of diazepam accelerated (reduced plasma concentration).

Digoxin: plasma concentration of digoxin possibly reduced.

Doxycycline: plasma doxycycline concentration possibly reduced.

Efavirenz: reduced plasma concentration of efavirenz (increase efavirenz dose).

* Fluconazole: accelerated metabolism of fluconazole

(reduced plasma concentration).

* Glibenclamide: possibly accelerated metabolism (reduced effect) of glibenclamide.

* Haloperidol: accelerated metabolism of haloperidol (reduced plasma haloperidol concentration).

* Hydrocortisone: accelerated metabolism of hydrocortisone (reduced effect).

*indinavir: metabolism accelerated by rifampicin (plasma indinavir concentration reduced, avoid concomitant use).

* Levonorgestrel: accelerated metabolism of levonorgestrel (reduced contraceptive effect).

Levothyroxine: accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism).

* Lopinavir: reduced plasma concentration of lopinavir (avoid concomitant use).

* Medroxyprogesterone: accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception).

* Nelfinavir: plasma concentration of nelfinavir significantly reduced (avoid concomitant use).

* Nevirapine: reduced plasma concentration of nevirapine (avoid concomitant use).

* Nifedipine: accelerated metabolism of nifedipine (plasma concentration significantly reduced).

* Norethisterone: accelerated metabolism of norethisterone (reduced contraceptive effect).

* Phenytoin: accelerated metabolism of phenytoin (reduced plasma concentration).

* Prednisolone: accelerated metabolism of prednisolone (reduced effect).

Propranolol: metabolism of propranolol accelerated (significantly reduced plasma concentration).

* Quinidine: accelerated metabolism of quinidine (reduced plasma quinidine concentration).

* Saquinavir: plasma concentration of saquinavir significantly reduced, avoid concomitant use.

* Verapamil: accelerated metabolism of verapamil (plasma concentration significantly reduced).

* Warfarin: accelerated metabolism of warfarin (reduced anticoagulant effect).

Zidovudine: avoidance of rifampicin advised by the manufacturer of zidovudine.

May increase the risk of hepatotoxicity when given with halothane or isoniazid.

May enhance the adverse effect, particularly bleeding, when given concomitantly with cefazolin and other cephalosporins containing N-methylthiotetrazole side chain.

Increased plasma concentrations with probenecid and trimethoprim-sulfamethoxazole.

Notes:

» Capsules should be swallowed whole. Avoid contact during dosing/preparation due to risk of contact sensitization.

» Patient advice Take dose at least 30 minutes before a meal, since absorption is reduced by food.

7.2.5. Antituberculosis Medicines

Antituberculosis treatment must always be with FDCs ± additional relevant individual drugs

7.2.5.1. Single medicines

Ethambutol (E)

ATC code: J04AK02

Tablet (dispersible), 100 mg (HCl), LOU 2

Tablet, 400 mg, LOU 2

Indications and dose

Treatment of TB, in combination with other medicines

Adult

TB (as part of a 6- or 8-month regimen), oral: 15 mg/kg daily or 30 mg/kg 3 times weekly; for retreatment, 25 mg/kg once daily for 60 days, then, 15 mg/kg once daily; recommended max dose: 1.6 g daily (regardless of weight)

Paediatric

Treatment of TB, in combination with other medicines, oral

Infant or **child** 20 mg/kg (range 15–25 mg/kg) once daily

Note: Serum ethambutol concentrations should be monitored. **Contraindications:** Hypersensitivity, optic neuritis, severe renal impairment, children under 5 years (unable to report symptomatic visual disturbances),

Precautions: Visual disturbances (Patients should report visual disturbances immediately and discontinue treatment), renal impairment (reduce dose and monitor plasma ethambutol concentration if CrCl is less than 30 mL/min, the elderly, breastfeeding

Renal impairment: Mild/moderate: reduce dose, if CrCl less than 30 mL/min monitor plasma ethambutol concentration. Severe: avoid.

Adverse effects: Optic neuritis (reduced visual acuity and red/green colour blindness (early changes usually reversible, prompt withdrawal may prevent blindness), gout, peripheral neuritis (especially in legs). Rare: Rash, pruritus, urticaria, thrombocytopenia. Frequency unknown: Nausea, vomiting, abdominal pain, GI upset, headache, dizziness, peripheral neuropathy, thrombocytopenia, eosinophilia, leucopenia, neutropenia. Potentially Fatal: Hepatotoxicity.

Interactions with other medicines:

The recent, concomitant, or subsequent use (without the recommended leflunomide washout period or procedure) of other agents known to induce hepatotoxicity may potentiate the risk of liver injury associated with leflunomide.

Using ethambutol together with atorvastatin may increase the risk of peripheral neuropathy, which is a potential side effect of both medications.

Decreased exposure with Aluminium hydroxide.

Notes:

- Ocular examination recommended before and during treatment
- Peak plasma concentration (measured 2–2.5 hours after dose) should be in the range 2–6 mg/L (7–22 micromol/L), trough (pre-dose) concentration should be less than 1 mg/L (4 micromol/L).

Isoniazid (H)

ATC code: J04AC01

Tablet, 100 mg, 300 mg, LOU 2

Tablet (scored), 50 mg, LOU 2

Injection, 100 mg/mL, LOU 4

Indications and dose

In combination with other medicines

Adult

TB (as part of a 6- or 8-month regimen), in combination with other medicines, oral: 5 mg/kg (4–6 mg/kg) daily (maximum, 300 mg daily), or 10 mg/kg (max 900 mg/day) 3 times weekly

TB, prophylaxis, oral: 300 mg daily for at least 6 months

Paediatric

Treatment of TB (in combination with other medicines), prophylaxis of TB, oral

Infant or **child older than 3 months:** 10 mg/kg (range 10–15 mg/kg) once daily (maximum 300 mg daily)

Contraindications: Drug-induced hepatic disease, hypersensitivity.

Precautions: Hepatic impairment, risk of peripheral neuritis (prophylactic pyridoxine recommended) in patients with malnutrition, chronic renal failure, diabetes mellitus or HIV infection, epilepsy, slow acetylator status, history of psychosis, porphyria, renal impairment.

Hepatic impairment: Use with caution, monitor liver function regularly and frequently in the first 2 months.

Renal impairment: Severe: reduce dose to maximum 4 mg/kg daily or 200 mg daily, risk of peripheral neuropathy.

Adverse effects: Nausea, vomiting, diarrhoea, GI pain, constipation, dry mouth.

Hepatotoxicity (withdraw treatment), peripheral neuropathy, blood disorders (including agranulocytosis, haemolytic anaemia, aplastic anaemia), optic neuritis, toxic psychoses, seizures, hypersensitivity reactions (including fever, rashes, joint pain, erythema multiforme and purpura), SLE-like syndrome, pellagra, hyper-reflexia, difficulty with micturition, hyperglycaemia, gynaecomastia.

Interactions with other medicines (*indicates serious):

Amitriptyline: increased plasma concentration of isoniazid.

Antacids (aluminium hydroxide, magnesium hydroxide): reduced absorption of isoniazid.

* Carbamazepine: increased plasma carbamazepine concentration and other antiepileptics (e.g., ethosuximide, primidone, phenytoin (also isoniazid hepatotoxicity possibly increased).

Cycloserine, clofazimine and warfarin: increased concentrations and risk of toxicity.

Diazepam: metabolism of diazepam and other benzodiazepines inhibited.

Halothane: possible potentiation of isoniazid hepatotoxicity.

Ketamine: possible potentiation of isoniazid hepatotoxicity.

Nitrous oxide: possible potentiation of isoniazid hepatotoxicity.

p-Aminosalicylic acid: increased plasma concentration of isoniazid.

Thiopental: possible potentiation of isoniazid hepatotoxicity.

Notes:

- **Patient Advice**. Isoniazid should be taken on an empty stomach, if taken with food to reduce GI irritation, oral absorption and bioavailability may be impaired
- Patients or their Caregivers should be explained on how to recognize signs of liver disease and be advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, weakness, malaise, jaundice or fatigue develop.

Pyrazinamide (Z)

ATC code: J04AK01

Tablet, 500 mg, LOU 2

Tablet (dispersible), 150 mg, LOU 2

Tablet (scored), 150 mg, LOU 2

Indications and dose

Adult

Treatment of TB, in combination with other medicines, oral

- For standard unsupervised 2-month treatment
  - <50 kg: 1.5 g daily
  - ≥50 kg: 2 g daily
- For intermittent supervised 2-month treatment
  - <50 kg: 2 g 3 times weekly
  - ≥50 kg: 2.5 g 3 times weekly

Paediatric

Treatment of TB, in combination with other medicines, oral

Infant or **child:** 35 mg/kg (range 30–40 mg/kg) once daily; maximum 2 g daily

Contraindications: Severe hepatic impairment, porphyria, hypersensitivity.

Precautions: Hepatic impairment, renal impairment, diabetes mellitus (monitor blood glucose, may change suddenly), gout, concurrent medications associated

with liver injury (particularly rifampicin).

Renal impairment: Severe impairment: reduce dose.

Hepatic impairment: Monitor hepatic function, idiosyncratic hepatotoxicity more common. Severe hepatic impairment: avoid use.

Adverse effects: Common: Nausea, vomiting. Rash, photosensitivity, pellagra. Rare: Flushing, dysuria, arthralgia, gout, sideroblastic anaemia, hepatotoxicity (including fever, anorexia, aggravation of peptic ulcer, hepatomegaly, splenomegaly, jaundice, liver failure).

Interactions with other medicines (*indicates serious):

- *Ciclosporin: reduced ciclosporin serum concentrations and potentially reduced
- immunosuppressive efficacy.
- Rifampicin: risk of severe hepatic injury.
- Zidovudine: decreased serum concentration and efficacy of pyrazinamide.
- Antagonises the effect of uricosuric agents (e.g., probenecid, sulfinpyrazone).
- May reduce the contraceptive effect of oestrogens.
- May inactivate oral typhoid vaccine.

Notes:

- Patients or their Caregivers should be told how to recognize signs of liver disease and be advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Rifampicin

ATC code: J04AB02

Capsule, 150 mg, 300 mg, LOU 2

Powder for injection, 600 mg, LOU 4

Treatment of TB, in combination with other medicines.

Indications and dose

Adult

TB (as part of a 6- or 8-month regimen), oral: 8–12 mg/kg once daily; usual dose: <50 kg: 450 mg daily, ≥50 kg: 600 mg daily

Paediatric

Treatment of TB, in combination with other medicines, oral

Infant or **child:** 15 mg/kg (range 10–20 mg) once daily; maximum 600 mg daily

Contraindications: Hypersensitivity to rifamycins, jaundice, concomitant use with saquinavir/ritonavir combination, atazanavir, darunavir, fosamprenavir, saquinavir, tipranavir.

Precautions: Hepatic impairment, liver function tests and blood counts required in liver disorders and on prolonged therapy, porphyria, discolours soft contact lenses. Patients on hormonal contraceptives should be advised to use additional means. Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, haemolysis or thrombocytopenia, discontinue permanently if serious adverse effects occur. Patients with current or history of alcoholism, risk factors of vitamin K deficiency (e.g., chronic liver disease, poor nutritional status, receiving prolonged antibacterial or anticoagulant therapy), diabetes mellitus, children and elderly, pregnancy and breastfeeding.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Impaired elimination, monitor liver function, avoid or do not exceed 8 mg/kg daily.

Adverse effects: Common Urine, tears, saliva and sputum coloured orange-red. Rare: Alterations of liver function, jaundice, potentially fatal hepatitis, anorexia, nausea, vomiting, diarrhoea, headache, drowsiness, rashes, fever, influenza-like syndrome, respiratory symptoms, collapse, shock, haemolytic anaemia, acute renal failure, thrombocytopenic purpura, oedema, muscular weakness, myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia, menstrual disturbances.

Interactions with other medicines (*indicates serious):

Abacavir: plasma concentration of abacavir possibly reduced.

Amitriptyline: plasma concentration of amitriptyline possibly reduced.

Antacids (aluminium hydroxide, magnesium hydroxide): reduced absorption of rifampicin.

Chloramphenicol: accelerated metabolism of chloramphenicol (reduced plasma chloramphenicol concentration).

* Ciclosporin: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).

* Contraceptives, oral: accelerated metabolism of estrogens and progestogens (reduced

contraceptive effect).

Dapsone: reduced plasma dapsone concentration.

* Dexamethasone: accelerated metabolism of dexamethasone (reduced effect).

Diazepam: metabolism of diazepam accelerated (reduced plasma concentration).

Digoxin: plasma concentration of digoxin possibly reduced.

Doxycycline: plasma doxycycline concentration possibly reduced.

Efavirenz: reduced plasma concentration of efavirenz (increase efavirenz dose).

* Fluconazole: accelerated metabolism of fluconazole (reduced plasma concentration).

* Glibenclamide: possibly accelerated metabolism (reduced effect) of glibenclamide.

* Haloperidol: accelerated metabolism of haloperidol (reduced plasma haloperidol concentration).

* Hydrocortisone: accelerated metabolism of hydrocortisone (reduced effect).

*indinavir: metabolism accelerated by rifampicin (plasma indinavir concentration reduced, avoid concomitant use).

* Levonorgestrel: accelerated metabolism of levonorgestrel (reduced contraceptive effect).

Levothyroxine: accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism).

* Lopinavir: reduced plasma concentration of lopinavir (avoid concomitant use).

* Medroxyprogesterone: accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception).

* Nelfinavir: plasma concentration of nelfinavir significantly reduced (avoid concomitant use).

* Nevirapine: reduced plasma concentration of nevirapine (avoid concomitant use).

* Nifedipine: accelerated metabolism of nifedipine (plasma concentration significantly reduced).

* Norethisterone: accelerated metabolism of norethisterone (reduced contraceptive effect).

* Phenytoin: accelerated metabolism of phenytoin (reduced plasma concentration).

* Prednisolone: accelerated metabolism of prednisolone (reduced effect).

Propranolol: metabolism of propranolol accelerated (significantly reduced plasma concentration).

* Quinidine: accelerated metabolism of quinidine (reduced plasma quinidine concentration).

* Saquinavir: plasma concentration of saquinavir significantly reduced, avoid concomitant use.

* Verapamil: accelerated metabolism of verapamil (plasma concentration significantly reduced).

* Warfarin: accelerated metabolism of warfarin (reduced anticoagulant effect).

Zidovudine: avoidance of rifampicin advised by manufacturer of zidovudine.

May increase the risk of hepatotoxicity when given with halothane or isoniazid. May enhance the adverse effect, particularly bleeding, when given concomitantly with cefazolin and other cephalosporins containing N-methylthiotetrazole side chain.

Increased plasma concentrations with probenecid and trimethoprim-sulfamethoxazole.

Notes:

» Take dose at least 30 minutes before a meal, as absorption is reduced when taken with food. Capsules should be swallowed whole. Avoid contact during dosing/preparation due to risk of contact sensitization

» Patients or their Caregivers should be told how to recognize signs of liver disease and be advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

7.2.5.2. Fixed-dose combinations

Rifampicin + Isoniazid (RH)

ATC code: J04AM02

Tablet, 150 mg + 75 mg, 150+100 mg, 300+150 mg, LOU 2

Tablet, 75 mg + 50 mg (children), LOU 2

Indications and dose

Treatment of TB (continuation phase)

Adult

Body weight up to 50 kg, oral: 450/300 mg daily for 4 months (continuation phase after 2-month initial phase), use RH 150/100 tablets, preferably taken before breakfast

Body weight 50 kg and above, oral: 600/300 mg daily for 4 months (continuation phase after 2-month initial phase), use FDC RH tablet 300/150 tablets, preferably taken before breakfast

Dose equivalence and conversion

FDC RH tablets contain rifampicin and isoniazid, the proportions are expressed in the form x/y where x and y are the strengths in milligrams of rifampicin and isoniazid, respectively.

Paediatric

Treatment of TB (continuation phase), oral

Child: FDC RH tablets are used in older children, provided the respective dose of each drug is appropriate for the weight of the child.

Dose equivalence and conversion

FDC RH tablets contain rifampicin and isoniazid; the proportions are expressed in the form x/y where x and y are the strengths in milligrams of rifampicin and isoniazid, respectively.

Contraindication, precautions, adverse effects, Interactions and notes:

Refer to individual medicines

Rifampicin + Isoniazid + Pyrazinamide (RHZ)

ATC code: J04AM05

Tablet, rifampicin 150 mg + isoniazid 75 mg + pyrazinamide 400 mg, LOU 2

Tablet, 75 mg + 50 mg + 150 mg (children), LOU 2

The properties listed below are those particular to the combination only. For the properties of the components, please see rifampicin, isoniazid, and pyrazinamide entries individually.

Indications and dose

For the initial intensive phase of the short-course treatment of pulmonary TB (in combination with ethambutol). Use FDC RHZ tablets, preferably taken before breakfast.

Adult

Body weight up to 39 kg, oral: 2 tablets daily for 2 months

Body weight 40–54 kg, oral: 3 tablets daily for 2 months

Body weight >55 kg, oral: 4 tablets daily for 2 months

Once the initial phase (2 months) is completed, continue treatment with the combination of rifampicin–isoniazid.

Paediatric

Initial treatment of TB (in combination with ethambutol)

Although not licensed in children, consideration may be given to use of FDC RHZ tablets in older children, provided the respective dose of each drug is appropriate for the weight of the child.

Dose equivalence and conversion

Tablet quantities refer to the number of FDC RHZ tablets, which should be taken. Each FDC RHZ tablet contains rifampicin 75 mg, isoniazid 50 mg, and pyrazinamide 150 mg.

Contraindication, precautions, adverse effects, interactions and notes: Refer to individual medicines.

Rifampicin + Isoniazid + Pyrazinamide + Ethambutol (RHZE)

ATC code: J04AM06

Tablet, 150 mg + 75 mg+400 mg + 275 mg, LOU 2

Indications and dose

Treatment regimen in the intensive phase for newly diagnosed TB. With weekly drug collection or directly observed treatment. Initial phase (2 months), use FDC RHZE tablets, preferably taken before breakfast.

Adult

TB meningitis and osteoarticular TB, oral: Two months of the below regimen for intensive phase combination (followed by 10 months of rifampicin + isoniazid FDC).

Body weight 30–39 kg, oral: 2 tablets daily for 2 months

Body weight 40–54 kg, oral: 3 tablets daily for 2 months

Above 55–69 kg body weight, oral: 4 tablets daily for 2 months

Over 70 kg body weight, oral: 5 tablets daily for 2 months

Dose equivalence and conversion

Tablet quantities refer to the number of FDC RHZE tablets, which should be taken. Each FDC RHZE tablet contains rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol 275 mg.

Paediatric

TB meningitis and osteoarticular TB, oral

Child (weight 5–20 kg): Use RHZ + single agent ethambutol

Child (weight 21–30 kg): Use RHZE FDC as per National TB guidelines, 2017 or later

Contraindication, precautions, adverse effects, interactions, and notes: Refer to individual medicines.

Rifapentine + Isoniazid (3HP)

ATC code: J04AM02

Tablet, 300mg + 300 mg, LOU 5

Indications and dose

Adult

Prevention of tuberculosis: 900/900mg (three tablets) Once weekly for a period of 3 months

Paediatric

Prevention of tuberculosis: Once weekly for a period of 3 months

Child >15 years: 900/900mg (three tablets) Once weekly for a period of 3 months

Contraindications: Hypersensitivity to rifapentine and isoniazid, acute liver disease, drug induced liver disease, previous liver damage due to rifapentine or isoniazid

Precautions: The elderly especially with evidence of hepatic impairment, Chronic liver disease, severe renal dysfunction, Restrict alcohol intake, intravenous drug users, peripheral neuropathy, patients hypersensitive to ethionamide, pyrazinamide and niacin. Patient with preexisting seizure disorders or psychosis. Patients with diabetes mellitus. Patient with porphyria

Hepatic impairment: Pharmacokinetics are very similar to normal volunteers in persons with mild to severe liver impairment.

Renal impairment: Refer to individual medicines.

Pregnancy: Use only if potential benefit outweighs possible risk

Breastfeeding: Present in breastmilk, use only if potential benefit outweighs possible risk

Adverse effects: Nephrotoxicity, reddish discoloration of body fluids, pyuria, cystitis, hyperuricemia, hyperkalemia, hypoglycemia, hyperphosphatemia, anemia, lymphadenopathy, rash, sweating, pruritis, hemoptysis, coughing, epistaxis, dyspepsia, nausea, vomiting , diarrhea, constipation, hemorrhoids, headaches, tremor, insomnia, anorexia, arthralgia, hypertension, conjunctivitis

Interactions with other medicines (*indicates serious): Protease inhibitors, elvitegravir, rilpivirine, etravirine, doravirine, artemisinin, any direct acting antiviral for chronic hepatitis C, antiepileptic agents, immunosuppressants like corticosteroids, coumarin derivatives, contraceptives

7.2.5.3. Medicines for treatment of MDR-TB

Treatment and care for drug-resistant TB has been decentralized in Kenya's 47 counties and 300 sub-counties. The implementation of the programmatic management of drug-resistant TB began in 2006 with injectable agents as core medicines in the treatment regimens and has rapidly evolved ever since based on WHO guidelines. In 2018, WHO recommended the use of injectable free regimens for the treatment of drug-resistant TB

Amikacin

ATC code: J01GB06

Injection, 1 g in vial, LOU 3

Indications and dose

Adult

Treatment of MDR-TB, in combination with other medicines, *IV or IM:* 15 mg/kg once daily (maximum 1 g), weight categorization:

- 33–50 kg: 500–750 mg
- 51–70 kg: 1000 mg
- >70 kg: 1000 mg

Paediatric: Not recommended in the current national TB management guidelines

Contraindications: Hypersensitivity to amikacin or aminoglycoside antibiotics, Myasthenia gravis. Concomitant or sequential administration of oral or topical drugs that are neurotoxic, ototoxic or nephrotoxic, concomitant use with potent diuretics.

Precautions: Patient with pre-existing vertigo, tinnitus, or hearing loss, vestibular damage, neuromuscular disorders (e.g., Parkinson's disease), hypocalcaemia. Dehydrated patients, renal impairment, premature infants, neonates, children and elderly, pregnancy and breastfeeding.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dosage adjustment is required in patients with renal impairment. Patients should receive the usual loading dose, however, subsequent doses and/or dosing intervals should be adjusted. Adjustment may be based on amikacin serum levels. Target amikacin serum levels for once daily dosing: pre-dose (trough) concentration should be < 5 mg/L.

Adverse effects: Significant: **Hypersensitivity, neurotoxicity, ototoxicity, nephrotoxicity, CDAD, pseudomembranous colitis (prolonged use)**, anaemia, eosinophilia, tinnitus, hypoacusis, vertigo, GI disturbances, pyrexia, injection site pain (IM), oliguria, azotaemia, RBC and/or WBC in urine, rash, pruritus, urticaria. fungal or bacterial superinfection. Rare: Albuminuria, arthralgia, impaired balance, hypotension, muscle twitching, tremor. Apnoea (respiratory paralysis), neuromuscular blockade, paralysis.

Interactions with other medicines:

Increased risk of nephrotoxicity and ototoxicity with vancomycin, amphotericin B, bacitracin, cisplatin, ciclosporin, cephaloridine, paromomycin, polymyxin B, colistin, tacrolimus, viomycin, IV mannitol, capreomycin or other aminoglycosides, Enhanced effects of respiratory paralysis with anaesthetics or neuromuscular blocking agents (e.g., tubocurarine, succinylcholine, decamethonium, atracurium, rocuronium, vecuronium, opioid analgesic, massive transfusions with citrated anticoagulated blood), suxamethonium, Antagonism of effect of pyridostigmine and neostigmine, Increased risk of ototoxicity with furosemide and ethacrynic acid., Incompatible with amphotericin chlorothiazide Na, erythromycin gluceptate, heparin, nitrofurantoin Na, phenytoin Na, thiopentone Na, warfarin Na, some penicillins and cephalosporins. May reduce antibacterial activity with penicillins.

Notes:

- Administration by IM injection or slow intermittent IV infusion over 30 minutes at a final concentration not to exceed 10 mg/mL. For IV infusion, dilute with glucose 5% or sodium chloride 0.9% or compound sodium lactate.
- Pre-dose (trough) concentration should be less than 5 mg/L for once daily dosing.

Amoxicillin + Clavulanic Acid (Co-Amoxiclav)

ATC code: J01CR02

Tablet, 875 mg + 125 mg (1 g), LOU 3

Indications and dose

Activity against TB, clavulanate is a beta-lactam inhibitor, and it is for its properties that it is used in combination with imipenem/cilastatin in treatment of MDR-TB in children.

Dose expressed in amoxicillin component

Paediatric

Child under 30 kg: 80 mg/kg/day in 2 divided doses. Maximum dose: 4000 mg daily

Contraindications: known hypersensitivity (allergy) to any penicillins or other β-lactams (e.g., cephalosporins, carbapenems, monobactams), Infectious mononucleosis (suspected or confirmed).

Renal impairment: Amoxicillin is renally excreted and the dose should be adjusted for renal failure. For CrCl 10–30 mL/min dose 1000 mg as amoxicillin twice daily, for CrCl <10 mL/min dose 1000 mg as amoxicillin once daily. It is cleared by dialysis, so should be dosed after dialysis – single dose every 24 hours and after each dialysis session.

Hepatic impairment: Clavulanate is cleared by the liver, so care should be used when using in patients with liver failure.

Pregnancy and breastfeeding: Probably safe in pregnancy (no known risk), can be used while breastfeeding.

Adverse reactions allergic reaction, specifically anaphylaxis (bronchospasm, sudden or severe decrease in blood pressure), anaphylactoid and SCARs (e.g., SJS, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms) skin rash, joint pain, fever, GIT reaction (mild diarrhoea, nausea, vomiting), oral candidiasis (sore mouth or tongue), pseudomembranous colitis (severe abdominal or stomach cramps and pain, abdominal tenderness, watery and severe diarrhoea), rarely, cholestatic hepatitis. tooth discolouration (brown, yellow, grey) particularly in children, vulvovaginal infection, elevated liver enzymes, changes in blood counts (prolonged therapy), convulsion (high doses), rarely, thrombocytopenia, leucopenia.

Interactions with other medicines: Decreased renal tubular secretion resulting in increased and prolonged serum concentration with probenecid. (except in cases of gonorrhea and other STD), Increased risk of allergic reactions (e.g., rashes) with allopurinol, tetracyclines, chloramphenicol, macrolides, and sulfonamides may interfere with the bactericidal effect of amoxicillin, may reduce the efficacy of oral contraceptives (e.g.,

estrogen/progesterone combination), may reduce the excretion and increase the toxicity of methotrexate methotrexate, may prolong PT or increase INR when used with oral anticoagulants, e.g., warfarin.

Notes:

- Good oral absorption, best tolerated and well absorbed when taken at the start of a standard meal.
- CSF penetration Approximately 5% of the plasma concentration reaches the CSF.

Bedaquiline (BDQ)

ATC code: J04AK05

Tablet, 100 mg, LOU 3

Indications and dose

Adult

Multiple-drug-resistant pulmonary TB, in combination with ≥3 other drugs, oral: Initially 400 mg once daily for 2 weeks, then 200 mg 3 times a week for 22 weeks (Monday, Wednesday and Friday), taken with food; intervals of at least 48 hours between each dose; continue appropriate combination therapy after bedaquiline. Administer by directly observed therapy.

If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From week 3 onward, if a 200-mg dose is missed, patients should take the missed dose as soon as possible, and then resume the 3 times a week regimen.

Paediatric: Not indicated for use in children

Contraindications: QTc interval more than 500 milliseconds (derived using Fridericia's formula), ventricular arrhythmia, hypersensitivity, concomitant use with moderate or strong CYP3A4 inducers.

Cautions: Hypothyroidism, QTc interval (derived using Fridericia's formula) 450–500 milliseconds, risk factors for QT interval prolongation (e.g., electrolyte disturbances, heart failure, history of symptomatic arrhythmias, bradycardia, congenital long QT syndrome)

Hepatic Impairment: Manufacturer advises caution in moderate impairment, avoid in severe impairment—no information available.

Renal Impairment: Manufacturer advises caution if eGFR less than 30 mL/min/1.73 m2.

Pregnancy: Manufacturer advises avoid unless potential benefit outweighs risk.

Breastfeeding: Manufacturer advises avoid—present in milk in animal studies.

Adverse effects: Common or very common: Arthralgia, diarrhoea, dizziness, headache, abnormal hepatic function (transient increase in serum transaminases (AST, ALT), increased serum amylase), myalgia, nausea, QT interval prolongation, vomiting, haemoptysis, rash. If syncope occurs, obtain ECG.

Interactions:

- Bedaquiline is metabolized by CYP3A4. Rifampicin (a CYP3A4 inducer) reduces bedaquiline in blood by half. Efavirenz based on a single dose study appears to reduce the amount of bedaquiline though inducing CYP3A4, which may result to treatment failure.
- CYP3A4 inhibitors (e.g., azole anti-fungal drugs, some macrolides, protease inhibitors, and many others) can raise the level of bedaquiline but can be considered for use if the benefits outweigh the risk.
- Avoid use with other drugs that prolong the QT interval as additive QT prolongation may occur (e.g., clofazimine, fluoroquinolones, delamanid, azole anti-fungal drugs, and many others), any syncopal event (fainting) should prompt an immediate medical evaluation and ECG.

Notes:

- **Monitoring requirements:**
  - Determine serum potassium, calcium, and magnesium before starting treatment (correct if abnormal)—remeasure if QT prolongation occurs during treatment.
  - Obtain ECG before starting treatment, and then at least monthly during treatment or more frequently if concomitant use with other drugs known to prolong the QT interval.
  - Monitor liver function before starting treatment and then at least monthly during treatment—discontinue treatment if severe abnormalities in liver function tests.
- **Patient and caregiver advice**:
  - Missed doses If a dose is missed during the first two weeks of treatment, the missed dose should not be taken and the next dose should be taken at the usual time, if a dose is missed during weeks 3–24 of treatment, the missed dose should be taken as soon as possible and then the usual regimen resumed.
  - Driving and skilled tasks Dizziness may affect performance of skilled tasks (e.g., driving).

Clofazimine (CFX)

ATC code: J04BA01

Capsules, 50 mg , 100 mg capsules, LOU 3

Indications and dose:

Treatment of MDR-TB, in combination with other medicines, oral

Adult

100 mg/day for 18 months (both the 6 months intensive phase and the 12 months continuation phase. Note: The daily dose is administered in 2 divided doses or once daily, depending on tolerance and available formulation.

Paediatric

Child under 30 kg: 2 to 3 mg/kg/day
Child over 30 kg: 100 mg/day for 18 months (both the 6 months intensive phase and the 12 months continuation phase. Note: The daily dose is administered in 2 divided doses or once daily, depending on tolerance and available formulation.

Precautions: Pre-existing GI symptoms (reduce dose, increase dose interval or discontinue if symptoms develop during treatment), liver and renal impairment, may discolour soft contact lenses, patients with risk factors for QT prolongation, history of depression, hepatic and severe renal impairment, pregnancy and breastfeeding.

Adverse effects: Reversible discoloration of skin, hair, cornea, conjunctiva, tears, sweat, sputum, faeces and urine, GI pain, nausea, vomiting, diarrhoea, weight loss, GI bleeding, severe mucosal and submucosal oedema, dry skin, acne-like eruptions, rashes, pruritus, photosensitivity, decreased sweat production, dry eyes. Rare: Headache, drowsiness, dizziness, taste disorders, elevation of blood glucose concentration. Potentially Fatal: Splenic infarction, GI bleeding.

Interactions with other medicines (*indicates serious):

- *Phenytoin: reduced phenytoin serum concentrations and loss of phenytoin efficacy.
- Increased risk of additive torsades de pointes and QT prolongation with other agents known to prolong QT interval (e.g., bedaquiline). May increase the serum concentrations of CYP3A4/5 substrates.

Notes:

- The drug is well tolerated and virtually non-toxic in the dosage used for multidrug therapy. The drug causes brownish black discoloration and dryness of skin. However, this disappears within a few months after stopping treatment. This should be explained to patients starting a multidrug therapy regimen for multibacillary leprosy.
- Skilled tasks: Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for about 24 hours.

Cycloserine (CS)

ATC code: J04AB01

Tablet, 250 mg and 125 mg[C], LOU 3

Indications and dose

Adult

Treatment of MDR-TB, in combination with other medicines, oral: 15–20 mg/kg daily for 18 months (both the 6-month intensive phase, followed by 12-month continuation phase)

- 33–50 kg: 500 mg
- 51–70 kg: 750 mg
- >70 kg: 750–100 mg

Paediatric

Treatment of MDR-TB, in combination with other medicines, oral

Child: 5–10 mg/kg twice daily (initially 5 mg/kg/dose and adjust according to blood concentration and response); maximum 1 g daily

Safety and effectiveness in paediatrics have not been established.

Contraindications: Epilepsy, depression, severe anxiety, psychosis, porphyria, severe renal impairment. Hypersensitivity.

Precautions: Neuropsychiatric status assessed at least monthly, more frequently if symptoms develop, renal impairment. Pregnancy and breastfeeding.

Renal impairment: Avoid use in all degrees of renal impairment

Adverse effects: Common: Neurological (headache, dizziness, vertigo, drowsiness, tremor, seizures, confusion, psychosis, depression), rash. Rare: Megaloblastic anaemia, changes in liver function tests, heart failure

Interactions with other medicines (*indicates serious):

- *Alcohol: increased risk of seizures.
- Ethionamide and Isoniazid: increased risk of CNS toxicity.
- Concomitant use with other anti-TB drugs may lead to vitamin B_{12} and/or folic acid deficiency, megaloblastic and sideroblastic anaemia. May inhibit hepatic metabolism of phenytoin.

Notes:

- Penetrates the cerebrospinal fluid.
- Serum concentration measurements aiming for a peak concentration of 20–35 mg/mL are often useful in determining the optimum dose for a given patient. Measure 3–4 hours after dose.

Delamanid (DLM)

ATC code: J04AK06

Tablet, 50 mg, LOU 3

Indications and dose

Adult

Multiple-drug-resistant pulmonary TB resistant to fluoroquinolones, in combination with other medicines, oral: 100 mg twice daily for 24 weeks, with appropriate combination therapy, followed by 14 months with appropriate combination therapy

Contraindications: QTc interval more than 500 milliseconds (derived using Fridericia's formula). Serum albumin less than 28 g/L, hypersensitivity, concomitant use with strong CYP3A4 inducers.

Precautions: Risk factors for QT interval prolongation (e.g., electrolyte disturbances, acute MI, heart failure with reduced left ventricular ejection fraction, severe hypertension, left ventricular hypertrophy, bradycardia, congenital long QT syndrome, history of symptomatic arrhythmias)

Hepatic Impairment: Manufacturer advises avoid in moderate to severe impairment.

Renal Impairment: Manufacturer advises avoid in severe impairment—no information available.

Conception and Contraception: Effective contraception required during treatment.

Pregnancy: avoid—toxicity in animal studies.

Breastfeeding: avoid—present in milk in animal studies.

Adverse effects: Common or very common: Anxiety, appetite decreased, asthenia, chest pain, cough, depression, dyslipidemia, dyspnoea, ear pain,

electrolyte imbalance, GI discomfort, haemoptysis, headache, hyperhidrosis, hypertension, hypotension, malaise, muscle weakness, nausea, oropharyngeal pain, osteochondrosis, pain, palpitations, peripheral neuropathy, photophobia, psychotic disorder, QT interval prolongation, reticulocytosis, sensation abnormal, skin reactions, sleep disorders, throat irritation, tinnitus, tremor, vomiting. Uncommon: Aggression, atrioventricular block, balance impaired, dehydration, delusional disorder, persecutory type, dysphagia, extrasystole, abnormal hepatic function, increased risk of infection, lethargy, leucopenia, oral paraesthesia, psychiatric disorders, thrombocytopenia, urinary disorders.

Interactions:

- Avoid concomitant administration of strong CYP3A inducers (e.g., rifampicin, carbamazepine), certain antimicrobials (e.g., clarithromycin, erythromycin, moxifloxacin), neuroleptics (e.g., phenothiazines, haloperidol), antiarrhythmics (e.g., amiodarone, quinidine), certain non-sedating antihistamines (e.g., terfenadine, astemizole), cisapride, droperidol, domperidone, methadone due to increased risk of QT interval prolongation. No clinically relevant reduction in delamanid exposure was observed with weak inducers.
- If co-administration of delamanid with any strong inhibitor of CYP3A (e.g., ritonavir, ketoconazole) is necessary, consider more very frequent monitoring of ECGs, throughout the delamanid treatment.
- Delamanid does not affect plasma exposure of coadministered anti- TB drugs, Rifater (isoniazid/rifampicin/pyrazinamide) + ethambutol in a clinically relevant manner (25% increase in ethambutol).
- Delamanid does not affect plasma exposure of antiretroviral drugs tenofovir, Kaletra (lopinavir/ritonavir), or efavirenz.
- Antiretroviral drugs, tenofovir, efavirenz, and Kaletra (lopinavir/ritonavir), do not affect delamanid exposure in a clinically relevant manner (24% increase).
- Avoid using with other drugs that prolong the QT interval as additive
- QT prolongation may occur (e.g., clofazimine, fluoroquinolones, bedaquiline, azole anti-fungal drugs, ondansetron, and several others).
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) are predicted to slightly decrease the exposure to delamanid.
- Antifungals, azoles (itraconazole, ketoconazole, voriconazole) very slightly increase the exposure to delamanid.
- Macrolides (clarithromycin) very slightly increase the exposure to delamanid.

Notes: Handling and Storage: Dispense in original container contains desiccant.

Monitoring requirements:

- Monitor serum albumin and electrolytes before starting treatment and then during treatment—discontinue treatment if serum albumin less than 28 g/L.
- Obtain ECG before starting treatment and then monthly during treatment (more frequently if serum albumin 28–34 g/L, or if concomitant use of potent CYP3A4 inhibitors, or if risk factors for QT interval prolongation, or if QTc interval 450–500 milliseconds in men or 470–500 milliseconds in women)—discontinue treatment if QTc interval more than 500 milliseconds (derived using Fridericia's formula).

Imipenem + Cilastatin

ATC code: J01DH51

Powder for injection, 250 mg (as monohydrate) + 250 mg (as sodium salt) in vial, LOU 3

Powder for injection, 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial, LOU 3

Indications and dose

Adult

Treatment of MDR-TB; added to complete regimen when any of the primary options cannot be used; must be used together with clavulanate, IV infusion: 1000 mg every 12 hours (dosed on the imipenem component); should be given with clavulanate (available as amoxicillin/clavulanate) 125 mg every 8–12 hours.

Paediatric: Not recommended; meropenem preferred

Contraindications: Carbapenem intolerance, meningitis (use meropenem rather than imipenem).

Precautions: Sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, renal impairment, CNS disorders, such as epilepsy, neutropenia

Hepatic disease: Elevated liver function tests have been noted in up to 6% of patients, but no definite liver damage has been documented.

Renal disease: Adjustment in dose based on severity of renal failure – for example, 750 mg every 12 hours for CrCl 20–40 mL/min, 500 mg every 12 hours for CrCl <20 mL/min. Dose after dialysis.

Pregnancy/breastfeeding: Little information is known regarding use in pregnancy, unknown safety during breastfeeding.

Adverse effects: Common: Nausea, vomiting, diarrhoea, local injection site reactions, e.g., phlebitis. Uncommon: Rash, pruritus, urticaria, taste alteration, fever, dizziness, somnolence, confusion, tremor, paraesthesia, headache, psychiatric disturbances, encephalopathy, convulsions (risk of convulsions is higher in people with pre-existing CNS disorders or renal impairment (especially when excessive doses are used). Imipenem is thought to have similar epileptogenic potential to high dose benzylpenicillin), hypotension, positive Coombs' test, increases in liver function tests and bilirubin, raised urea and creatinine,

CDAD, itch, rash. Rare: Red discoloration of the urine in children, anaphylaxis, hepatitis, SJS, angioedema, tachycardia, renal toxicity, blood dyscrasias.

Interactions with other medicines (*indicates serious):

- Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).
- Typhoid Live vaccines: decreased immunological response to the typhoid vaccine. Suggestion: allow 24 hours or more to elapse between the last dose of antibiotic and the administration of oral live typhoid vaccine.
- Valproic acid: decreased valproic acid plasma concentrations and loss of anticonvulsant effect.
- May induce generalised seizures with ganciclovir. Increased plasma concentration and half-life with probenecid. May increase anticoagulant effect of warfarin.

Notes:

- Route of administration IV or IM (total recommended IM dose is not more than 1.5 g/day and therefore route not very practical for treatment of drug-resistant TB)
- Suitability of this preparation for IV or IM administration varies dependent on product. Check product and instructions carefully. The IM preparation must not be administered intravenously, and the infusion preparation must not be administered intramuscularly. A Lyophilized powder 1:1 ratio of imipenem and cilastatin. Vials available as 250 mg, 500 mg, 750 mg, or 1 gram and contain equal amounts of both drugs. (i.e., a "500-mg vial" contains 500 mg of imipenem and 500 mg cilastatin).
- Storage: Powder should be kept at room temperature (15–25 °C), suspended product should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated.
- **Administration:** Follow manufacturers instructions dependent on product. Caution: complex administration. Reconstitute with 10 mL NaCl 0.9% to form a cloudy suspension. Do not administer this suspension without further dilution. Further dilute to 5 mg/mL with a compatible fluid to give a clear solution. 500 mg or less: over 20–30 minutes. More than 500 mg: over 40–60 minutes.
- CSF penetration: Good CSF penetration, but children with meningitis treated with imipenem had high rates of seizures (meropenem preferred for meningitis and for children).
- **Monitoring**: Symptomatic monitoring

Levofloxacin (LFX)

ATC code: J01MA12

Tablet (dispersible), 100 mg[C], LOU 3

Tablet, 250 mg, 750 mg, LOU 3

Tablet, (scored) 500 mg, LOU 3

Indications and dose

Adult

Dose in MDR-TB management: 750 mg daily; if weight >70 kg 750–1000 mg; comprises both the 6-month intensive phase regimen and the 12-month continuation phase

Paediatric

The following doses, based on body weight, may be given orally or intravenously for 60 days

Child < 50 kg: 8 mg/kg (maximum 250 mg) every 12 hours

Child 50 kg or more: 500 mg once every 24 hours

Contraindications: Hypersensitivity to levofloxacin or other quinolones. Epilepsy, history of tendon disorders related to previous fluoroquinolone use.

Precautions: Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment. Health-care workers should be aware that: quinolones are contraindicated in patients with a history of tendon disorders related to quinolone use, elderly patients are more prone to tendonitis, the risk of tendon rupture is increased by the concomitant use of corticosteroids, if tendinitis is suspected, the quinolone should be discontinued immediately. Patient with history of prolonged QT interval, uncorrected electrolyte disorders (e.g., hypokalaemia), risk factors that predispose to seizures or lower the seizure threshold, pre-existing aortic aneurysm and/or dissection, latent or actual defects in G6PD, diabetes mellitus, history or risk factors of psychiatric disorders, severe underlying diseases (e.g., sepsis), haemoptysis (inhalation). Renal impairment. Children and elderly. Pregnancy and breastfeeding.

Adverse Effects: Symptomatic hyperglycaemia and/or hypoglycaemia have been reported, usually in diabetics who are also taking hypoglycaemics or insulin. Such patients should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, levofloxacin should be stopped. CNS effects including seizures, increased intracranial pressure, lightheadedness, dizziness, tremor, psychotic reactions (e.g., hallucinations, nervousness, delirium), sensory or sensorimotor peripheral neuropathy, prolonged QT interval, phototoxicity, superinfection (prolonged use), bronchospasm, cough or productive cough, haemoptysis, fluoroquinolone-resistant *P. aeruginosa* (inhalation), exacerbation of myasthenia gravis, interstitial nephritis, acute renal insufficiency or failure, hypotension (rapid or bolus IV infusion). Rare: tendinitis, tendon rupture, suicidal thoughts, self-endangering behaviour, crystalluria, cylindruria, torsades de pointes, SJS, toxic epidermal necrolysis, hepatic necrosis, pancytopenia, agranulocytosis, haemolytic or aplastic anaemia, leukopenia, eosinophilia. Dyspnoea, chest pain, arrhythmia. Diarrhoea, vomiting, nausea, dyspepsia, constipation, abdominal pain, hepatitis, jaundice. Potentially Fatal: Hypersensitivity reactions (e.g., angioedema, anaphylactic shock), CDAD (e.g., pseudomembranous colitis), hypoglycaemic coma, severe hepatotoxicity.

Interactions with other medicines: Use of levofloxacin with drugs that alter blood-glucose concentrations

increases the risk of blood-glucose disturbances. Decreased absorption with iron salts, zinc containing multivitamins, Magnesium- or Aluminium-containing antacids, didanosine. Decreased bioavailability with sucralfate. Increased risk of CNS stimulation and seizures with drugs which may affect seizure threshold (e.g., theophylline, NSAIMs). Decreased renal clearance with cimetidine and probenecid due to blockage of renal tubular secretion of levofloxacin. May increase the half-life of ciclosporin. Increased INR and/or bleeding with vitamin K antagonists (e.g., warfarin). Increased risk of severe tendon disorders with corticosteroids. Increased risk for QT interval prolongation with class IA and III antiarrhythmics, TCA, macrolides and antipsychotic agents.

Notes:

- Since fluoroquinolones can cause degenerative changes in weight-bearing joints of young animals they should only be used in children and adolescents where their use may be justified if the benefits outweigh the risks.
- In the USA levofloxacin is licensed for use in children 6 months of age and older only for treatment and postexposure prophylaxis of inhalation anthrax.

Linezolid

ATC code: J01XX08

Tablet (dispersible), 150 mg[C], LOU 3

Tablet, 600 mg, LOU 3

Indications and dose

Drug-resistant TB as a primary regimen drug for the intensive phase of treatment (6 months) in an appropriate combination, oral

Adult

33–50 kg: 300 mg daily; >50 kg: 600 mg daily (if there is a severe adverse drug reaction, reduce to 300 mg)

Paediatric

Neonates up to 7 days old: 10 mg/kg every 12 hours, increasing to every 8 hours if response is poor

Neonate and child 7 days to 12 years: 10 mg/kg (to a maximum of 600 mg) every 8 hours

Child 12 to 18 years: Usual adult doses

Contraindications: Unless facilities for close observation and BP monitoring, avoid use in patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis, carcinoid syndrome, bipolar depression, schizoaffective disorder, acute confusional states. Patients with gram-negative bacterial infections. Concomitant use with MAOI or within 2 weeks of discontinuing MAOI, SSRIs, TriCyclic Antidepressants, selective serotonin- and norepinephrine-reuptake inhibitors, or other serotonergic drugs (e.g., bupropion, vilazodone, mirtazapine, amoxapine, buspirone, maprotiline, meperidine, trazodone, nefazodone), dopamine, dobutamine, epinephrine, norepinephrine, pseudoephedrine.

Precautions: Patients with pre-existing myelosuppression, history of seizure, Diabetes Mellitus, phenylketonuria, mixed (gram+ve and gram-ve) infections. Severe renal impairment. Pregnancy and breastfeeding.

Pregnancy: use only if potential benefit outweighs risk—no information available.

Breastfeeding: avoid—present in milk in animal studies.

Hepatic impairment: caution in severe impairment (no information available).

Renal impairment: metabolites may accumulate if eGFR less than 30 mL/min/1.73 m2.

Adverse Effects: Common**:** Anaemia, constipation, diarrhoea, dizziness, GI discomfort, headache, hypertension, increased risk of infection, insomnia, localised pain, nausea, skin reactions, taste altered, vomiting. Uncommon: Arrhythmia, chills, dry mouth, eosinophilia, fatigue, gastritis, hyperhidrosis, hyponatraemia, leucopenia, neutropenia, oral disorders, pancreatitis, polyuria, renal failure, seizure, thirst, thrombocytopenia, thrombophlebitis, tinnitus, tongue discolouration, transient ischaemic attack, vision disorders, vulvovaginal disorder. Rare or very rare: Antibiotic associated colitis, bone marrow disorders, tooth discolouration. Frequency not known: Alopecia, angioedema, lactic acidosis, nerve disorders, serotonin syndrome, SCARs

Interactions with other medicines: May reduce serum levels with rifampicin and phenytoin. May cause hypoglycaemia with insulin or oral antidiabetics. May increase risk of seizures with tramadol. **Potentially Fatal:** Increased risk of serotonin syndrome with MAOIs, SSRIs, TCAs, selective serotonin- and norepinephrine-reuptake inhibitors, or other serotonergic drugs (e.g., bupropion, vilazodone, mirtazapine, amoxapine, buspirone, maprotiline, meperidine, trazodone, nefazodone). Significant increase in BP with vasopressive agents (e.g., epinephrine, norepinephrine), sympathomimetic agents (e.g., pseudoephedrine) and dopaminergic agents (e.g., dopamine, dobutamine).

Notes:

- **Optic neuropathy:** Severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. Patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and colour vision) immediately, patients experiencing new visual symptoms (regardless of treatment duration) should be evaluated promptly, and referred to an ophthalmologist if necessary, visual function should be monitored regularly if treatment is required for longer than 28 days.
- **Blood disorders**: Haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) have been reported in patients receiving linezolid. It is recommended that full blood counts are monitored weekly. Close monitoring is recommended in patients who: receive treatment for more than 10–14 days, have pre-existing myelosuppression, are receiving drugs that may have adverse effects on haemoglobin, blood counts, or platelet function, have

severe renal impairment. If significant myelosuppression occurs, treatment should be stopped unless it is considered essential, in which case intensive monitoring of blood counts and appropriate management should be implemented.

Moxifloxacin

ATC code: J01MA14

Tablet (dispersible), 100 mg[C], LOU 3

Tablet, 400 mg, LOU 3

Indications and dose

Drug-resistant TB as one of the primary regimen drugs as an alternative to levofloxacin, oral: 400 mg daily across all weight classes

Paediatric

Quinolones cause arthropathy in the weight-bearing joints of immature animals and are therefore generally not recommended for use in children and growing adolescents. However, the significance of this effect in humans is uncertain and in some specific circumstances, short-term use in children may be justified, e.g., for treatment and prophylaxis of inhalational anthrax.

Contraindications: Hypersensitivity to moxifloxacin or other quinolone antibiotics. Patient with history of tendon disorders, myasthenia gravis, QT interval prolongation, ventricular arrhythmias, proarrhythmic conditions (e.g., bradycardia, acute MI), peripheral neuropathy, uncorrected electrolyte disorders (e.g., hypokalaemia, hypomagnesemia). Concomitant use with Class 1A and Class III antiarrhythmics, antihistamines, and other drugs that prolong QT interval (e.g., cisapride, erythromycin, antipsychotics, and TCA).

Precautions: Patient with known or suspected CNS disorders (e.g., seizure disorder) or other risk factors predisposing to seizures, solid organ transplant recipients, significant bradycardia or acute myocardial ischaemia, diabetes mellitus, rheumatoid arthritis, G6PD, psychiatric disease. Renal and hepatic impairment. Elderly. Pregnancy and breastfeeding.

Adverse Effects: GI disturbances include nausea, vomiting, diarrhoea, abdominal pain, and dyspepsia and are the most frequent adverse effects. Pseudomembranous colitis, pancreatitis, and dysphagia have been reported rarely. Hypersensitivity reactions (e.g., anaphylaxis, shock). Superinfections, hyperglycaemia, CDAD, irreversible tendinitis, tendon rupture. Headache, dizziness, confusion, insomnia, and restlessness are among the commonest effects on the CNS. Eye irritation, conjunctivitis, decreased visual acuity, eye pain and discomfort, eye pruritus, lacrimation, ocular hyperemia, subconjunctival haemorrhage, xerophthalmia. Rash, pruritus. Others include: tremor, drowsiness, nightmares, visual and other sensory disturbances, hallucinations, psychotic reactions, depression, convulsions, and intracranial hypertension. Paraesthesia and peripheral neuropathy have also been reported. **Potentially Fatal:** Hypoglycaemia, fulminant hepatitis. Rare: QT prolongation and ventricular arrhythmias (including torsades de pointes), bullous skin reactions (e.g., SJS, toxic epidermal necrolysis).

Interactions with other medicines: Increased risk of bradycardia with potassium-reducing agents (e.g., loop diuretics). Increased risk of tendon disorder with corticosteroids. Decreased absorption by forming chelates with antacids containing Al, Mg, Fe, sucralfate and multivalent cations. May enhance anticoagulant effects of warfarin. **Potentially fatal:** Increased risk of QT prolongation with class IA (e.g., quinidine) and class III (e.g., amiodarone) antiarryhthmics, terfenadine, cisapride, erythromycin, antipsychotics (e.g., haloperidol), and TCA (e.g., amitriptyline).

P-Aminosalicylic Acid(Pasa -Aminosalicylic Acid [4-ASA])

ATC code: J04AA01

Granules, 4 g in sachet, LOU 3

Indications and dose

Treatment of MDR-TB, in combination with other medicines; used to complete regimen if any of the primary drugs cannot be used, oral:

- 33–50 kg: 8 g daily
- 51–70 kg: 8 g daily
- >70 kg: 8–12 g daily

Paediatric

Treatment of MDR-TB, in combination with other medicines, oral

Child: 200–300 mg/kg per day in 2–4 divided doses; maximum 10 g daily

Contraindications: Hypersensitivity to aminosalicylic acid products, end-stage renal disease (ESRD).

Precautions: Glucose-6-phosphate dehydrogenase (G6PD) deficiency (risk of haemolysis), hepatic impairment, peptic ulcer disease, renal impairment, congestive heart failure, patients on therapy of more than 1 month should be considered for maintenance vitamin B12. Pregnancy, breastfeeding, sodium salt in heart failure, gastric ulcer. Monitor patient closely for 1st 3 months of treatment and counsel to report: sore throat, fever, unusual bleeding or bruising, persistent nausea or vomiting, or abdominal pain.

Renal impairment: Not recommended to be used in patients with severe renal impairment.

Hepatic impairment: Use with caution. Increase laboratory and clinical monitoring. Dose reduction is not considered necessary.

Adverse effects: Common Nausea, vomiting, diarrhoea, abdominal pain.

Rare Hepatotoxicity, haemolysis, fever, rash, blood dyscrasias (agranulocytosis, haemolytic anaemia, leucopenia, thrombocytopenia), hypoglycaemia, crystalluria, encephalopathy, thyroid goitre, hypoglycaemia, pericarditis, vasculitis.

Interactions with other medicines (*indicates serious):

Digoxin: reduced digoxin serum concentrations.

Ethionamide: excessive adverse effects (GI distress and hepatotoxicity).

Isoniazid: reduction in the acetylation of isoniazid

(increased isoniazid levels).

Vitamin B12: reduced absorption of vitamin B12.

Additive adverse effects of aminosalicylates and salicylates, probenecid may increase toxicity by delaying renal excretion and enhancing plasma concentrations of aminosalicylate, activity of aminosalicylic acid may be antagonised by ester-type local anaesthetics such as procaine, may enhance effect of oral anticoagulants (may need to adjust dose), ammonium chloride may increase risk of crystalluria (do not use concurrently).

Notes:

- Second-line medicines should be reserved for treating MDR-TB and should be used in specialized centres adhering to WHO standards for TB control.
- Patient advice: Should be taken with acidic food or drink (yoghurt, apple sauce or fruit juice).
- Granules should be stored in the refrigerator. Can be stored at room temperature for short periods of time.
- Do not use granules if the packet is swollen or the granules have lost their tan colour and have turned dark brown or purple.
- Sprinkle granules on applesauce or yogurt or suspend in tomato, orange, grapefruit, grape, cranberry, apple or fruit juice containing drinks.
- Patients should be advised that the skeleton of the granules may be seen in the stool

Prothionamide (Protionamide) (PTO)

ATC code: J04AD01

Tablet, 250 mg, LOU 3

Indications and dose

Treatment of drug-resistant TB, given to complete regimen if any of the primary drugs cannot be used

Adult

Drug-resistant TB, oral: 15 to 20 mg/kg daily (maximum 1 g daily); typically treatment in such patients is given in divided doses with meals, or as a single daily dose. Once-daily dosing is preferred to maximise peak levels, particularly for daily doses ≤750 mg. Consider twice-daily dosing if patients are unable to tolerate once-daily regimens.

- 33–50 kg: 500 mg
- 51–70 kg: 750 mg
- >70 kg: 750–1000 mg

Prothionamide should be taken with or after meals to reduce GI adverse effects. Most patients also require gradual dose escalation: initially 250 mg once a day, increasing by 250 mg every 3 to 5 days. All patients must be put on pyridoxine while receiving prothionamide.

Paediatric

Drug-resistant TB, oral

15–20 mg/kg (max. 1 g) once daily, oral

Once-daily dosing is preferred to maximise peak levels, particularly for daily doses ≤750 mg. Consider twice-daily dosing if patients are unable to tolerate once-daily regimens.

Contraindications: Hypersensitivity. Severe hepatic disease, porphyria.

Precautions: Should not be used in severe hepatic impairment. Liver function tests should be carried out before, and regularly during, treatment with ethionamide.

Caution is necessary in patients with depression or other psychiatric illness.

Difficulty may occur in the management of diabetes mellitus. Periodic monitoring of blood glucose, thyroid function, and visual function is desirable.

TFTs: 3 monthly (if being given in combination with PAS increase to monthly)

Blood glucose should be monitored regularly in patients with diabetes (risk of hypoglycaemia). Pregnancy and breastfeeding.

Adverse effects: Nausea, vomiting, depression and hallucinations. Rare: jaundice, menstrual disturbance and peripheral neuropathy

- Hepatic: Transient increases in LFTs. Serious: Acute hepatitis (rare).
- GI: Nausea, vomiting, diarrhoea, anorexia, excessive salivation, metallic taste, stomatitis, and abdominal pain.
- Neurological (maybe increased in combination with cycloserine): Dizziness, encephalopathy, peripheral neuropathy.
- Ophthalmic: Optic Neuritis (rare).
- Psychiatric: Psychotic disturbances, depression. Thrombocytopenia. Peripheral and/or optic neuritis.
- Metabolic: Gynaecomastia, hypoglycaemia, hypothyroidism.

Notes:

- Active only against mycobacteria including *Mycobacterium tuberculosis*, M. kansasii, M. leprae, M. malmoense, and some strains of M. avium complex.
- Resistance develops rapidly if used alone and there is complete cross-resistance between ethionamide and Prothionamide.
- Cross-resistance has also been reported with isoniazid and within vitro thioacetazone.

Terizidone (TRD)

ATC code: J04AK03

Tablet, 300 mg, LOU 3

Indications and dose

Adult

Second-line agent for MDR-TB, oral: Initially 250 mg to 500 mg per day (oral in one or two divided doses), increased to 1000 mg per day (in two divided doses, or once a day if tolerated) depending on cycloserine serum concentrations.

The usual target dose is 15–20 mg/kg/day; maximum 1 g per day. Avoid high-fat meals at the time of taking terizidone.

- 33–50 kg: 500 mg
- 51–70 kg: 750 mg
- >70 kg: 750–1000 mg

Paediatric

Second-line agent for MDR-TB, oral

Child: Target dose is 10–20 mg/kg/day, given in two divided doses; maximum 1 g per day. All patients must be prescribed pyridoxine while receiving terizidone. The usual dose ranges from 50 to 100 mg daily, up to 50 mg per 250 mg of terizidone.

Contraindications: Hypersensitivity: To cycloserine or terizidone. Neurological disorders: Epilepsy, depression, severe anxiety, psychotic states. Alcohol Dependence.

Renal Disease: Severe renal impairment.

Precautions: Pregnancy and Breastfeeding. Neurological: Stop or reduce dose if symptoms of CNS toxicity such as convulsions, psychosis, suicidal tendencies, somnolence, depression, confusion, hyper-reflexia, headache, tremor, vertigo, paresis or dysarthria develop. Dermatological: Stop or reduce dose if allergic dermatitis develops.

Renal impairment: Use with caution. Reduce dose if CrCl < 30 mL/min, to 250 mg once daily or intermittently 500 mg on three days per week (for example Monday, Wednesday and Friday). Dialysis patients should take terizidone after dialysis sessions. There are insufficient data to determine whether terizidone is clinically effective in people undergoing continuous forms of dialysis (e.g., continuous peritoneal dialysis).

Adverse effects: Common: Neurological: Confusion, disorientation, dizziness, somnolence (increased risk if peak serum level >35 mg/L). Serious: Cardiovascular: Cardiac arrhythmias, and sudden development of congestive heart failure (rarely reported at doses greater than 1 to 1.5 g daily). Dermatological: Rash and photosensitivity, SJS (rare). Haematological: Vitamin B12 and/or folic acid deficiency, megaloblastic anaemia or sideroblastic anaemia (rare). Psychiatric: Depression, seizure, psychotic disturbances (increased risk if peak serum level >35 mg/L).

Interactions with other medicines:

Alcohol: Increased risk of convulsions with terizidone.

Isoniazid: Increased risk of CNS toxicity when given with terizidone.

High fat meals: Delayed and reduced absorption of terizidone.

Notes:

Drug level monitoring (indications): Ensure therapeutic dose, but toxic levels are not reached. Renal impairment and if patients are switched to terizidone from cycloserine

Target Level of cycloserine: 20 – 35 mg/L (peak)

Timing of sample:

- Peak: 2 hours post dose. Repeat at 6 hours if delayed absorption is suspected.
- Trough levels: taken immediately prior to a dose.

Frequency of Levels:

- Serum levels after 7 days at target dose.
- Repeat fortnightly for one month and until stable. Serum levels may increase over a 2-week period despite a stable dose due to accumulation of cycloserine.
- Repeat at least 6 monthly.
- Repeat if malabsorption, treatment failure, or neuropsychiatric adverse effects (should be monitored monthly) are suspected.
- Patients with reduced renal function require more frequent monitoring, initially weekly until stable.

Suggested Actions:

- High Peak Level: Reduce dose if level >35 mg/L.
- If level is 35 to 50 mg/L, consider reducing dose by 25% per day.
- If level >50 mg/L, consider halving the dose. Recheck level after four days.

Pretomanid

ATC code: J04AK08

Tablet, 200mg, LOU 3

Indications and dose

Adult

In combination with bedaquiline, linezolid and moxifloxacin (BPaLM) for the treatment of pulmonary Extensive drug resistant (XDR)or treatment intolerant multidrug resistant (MDR)TB : Dose details 200mg once daily for 26 weeks.

Note: longer duration therapy may be considered in patients who have not responded to therapy at 26 weeks on a case to case basis. To be taken with food

Contraindications: Hypersensitivity to pretomanid or other nitroimidazoles

Precautions: Avoid alcohol, Modification or interruption of linezolid dosing maybe needed during therapy to manage toxicity

Hepatic impairment: Safety in patients with hepatic impairments has not been established

Renal impairment: Safety in patients with renal impairments has not been established

Pregnancy: Limited data, use if benefits outweigh potential risks

Breastfeeding: Unknown whether excreted in human milk, use if benefits outweigh potential risks

Adverse effects: Hepatotoxicity, QT prolongation (as BPaLM), anemia, decreased appetite, hypoglycemia, lactic acidosis, insomnia, anxiety, depression, peripheral neuropathy, headache, dizziness, visual impairment, eye pruritis, hypotension, cough, hematemesis, nausea vomiting, dyspepsia, musculoskeletal pain, fatigue, asthenia.

Interactions with other medicines: CYP3A4 inhibitors and inducers

Notes: Pretomanid should be administered only in combination with bedaquiline (400mg once daily for two weeks followed by 200mg three times a week, with at least 48 hours between doses, orally for a total of 26 weeks) and linezolid (1200mg daily orally for up to 26 weeks)

7.3. Antifungal Medicines

Amphotericin B

ATC code: J02AA01

Powder for injection: 50 mg in vial as deoxycholate and as Liposomal, LOU 4

Indications and dose

Life-threatening fungal infections including histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, aspergillosis, chronic mycetoma, cryptococcosis, mucormycosis, sporotrichosis, candidiasis and visceral leishmaniasis.

Adult

Systemic fungal infections, by IV infusion: For deoxycholate form, Initial test dose, 1 mg over 20–30 minutes, followed by a 30-minute observation period. Dosing should start at 250 micrograms/kg daily, gradually increased up to 1 mg/kg daily, or in severe infection, up to but not more than 1.5 mg/kg daily or on alternate days. Administration should be over 2–6 hours, where slower infusion may reduce adverse effects.

For liposomal form, initial test dose 1mg over 10 minutes, then 3mg/kg once daily, maximum 5mg/kg

Note: Prolonged treatment is usually necessary, if treatment is interrupted for longer than 7 days, it should be recommenced at 250 micrograms/kg daily and increased gradually.

Liposomal form to be used in severe systemic mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional deoxycholate form

Paediatric

Conventional amphotericin B (as deoxycholate)

Systemic fungal infections, IV infusion

Neonate, infant, or **child:** Initial test dose of 100 micrograms/kg (maximum 1 mg) included as part of first dose, then 250 micrograms/kg daily, gradually increased up to 1 mg/kg daily or in severe infection, up to maximum of 1.5 mg/kg daily.

For prolonged treatment, which is usually necessary, a higher dose (maximum 1.5 mg/kg) may be given on alternate days. If treatment is interrupted for longer than 7 days, recommence at 250 micrograms/kg daily and increase gradually.

Contraindications: Known hypersensitivity.

Precautions: Close medical supervision throughout treatment and initial test dose required (see Anaphylaxis, below), renal impairment, hepatic and renal function tests, blood counts and plasma electrolyte (including potassium and magnesium concentration) monitoring, avoid rapid infusion (risk of arrhythmias).

Anaphylaxis occurs rarely with IV amphotericin B and a test dose is advisable before the first infusion. The patient should be observed for at least 30 minutes after the test dose. Prophylactic antipyretics or hydrocortisone should only be used in patients who have previously experienced acute adverse reactions (in whom continued treatment with amphotericin B is essential).

Renal impairment: Mild to severe: use only if no alternative. No dosage reduction is necessary, but further impairment is likely with conventional (as deoxycholate) amphotericin B. Nephrotoxicity may be reduced with use of liposomal formulations. Consider sodium replenishment to reduce nephrotoxicity.

Hepatic impairment: Dose reduction not necessary. Discontinue if LFTs – ALP, Bilirubin are elevated while on treatment.

Adverse effects: Similar for all amphotericin B formulations, the rates may depend on the formulation and infusion rate, liposomal formulations are generally better tolerated.

- Common: Fever, headache, nausea and vomiting, anorexia, hypokalaemia, hypomagnesaemia, diarrhoea, dyspnea, epigastric pain, muscle and joint pain, infusion reactions (see below), hypotension thrombophlebitis, anaemia, nephrotoxicity (see below).
- Hypertension, cardiac arrest, arrhythmias (rapid infusion of conventional amphotericin B), blood dyscrasias, GI bleeding, elevated liver enzymes, hepatotoxicity, rash, neurological effects (e.g., seizures, confusion, blurred vision, hearing loss, tinnitus).
- Rare: Anaphylactoid reactions, hyperkalaemia (especially in renal impairment), cardiovascular toxicity (including arrhythmias, ECG changes).
- Nephrotoxicity: Conventional (as deoxycholate) amphotericin B affects renal function in all patients, changes are dose related and generally reversible (except with cumulative doses > 3–5 g).
- Infusion reactions: Include fever, chills, hypotension, anorexia, nausea, vomiting, headache, malaise, muscle and joint pain, usually lessen with continued treatment.
- Continuous infusion of conventional (as deoxycholate) amphotericin B reduces infusion reactions.

Interactions with other medicines (*indicates serious):

Amphotericin B is nephrotoxic, administration with other nephrotoxic drugs or cytotoxic drugs/ antineoplastic agents may cause additional renal impairment.

It may also reduce potassium concentration, administration with other drugs with this effect may worsen hypokalaemia. Monitor potassium concentration, supplements may be needed.

Amikacin: increased risk of nephrotoxicity.

Amiloride: increased risk of adverse effects

Acyclovir: Increased risk of nephrotoxicity

Azoles (e.g., fluconazole): possible antagonistic effect, potentially reduced antifungal efficacy.

- Ciclosporin: increased risk of nephrotoxicity.
- Dexamethasone: increased risk of

hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions).

» Digoxin: hypokalaemia caused by amphotericin B increases cardiac toxicity of digoxin.

Fluconazole: possible antagonism of effect of amphotericin B.

Flucytosine: renal excretion of flucytosine decreased and cellular uptake increased (flucytosine toxicity possibly increased).

Furosemide: increased risk of hypokalaemia.

Gentamicin: increased risk of nephrotoxicity.

Hydrochlorothiazide: increased risk of hypokalaemia.

» Hydrocortisone: increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions).

Miconazole: possible antagonism of effects of amphotericin B.

Paromomycin: possible increased risk of nephrotoxicity.

Pentamidine: possible increased risk of nephrotoxicity.

» Prednisolone: increased risk of hypokalaemia (avoid concomitant use unless prednisolone needed to control reactions).

Streptomycin: increased risk of nephrotoxicity.

Vancomycin: possible increased risk of nephrotoxicity.

Notes:

» Check renal function before starting treatment, monitor renal function and electrolytes (especially potassium, magnesium and sodium) at least three times a week and complete blood picture and hepatic function twice a week during treatment and until stable after treatment stops.

» Conventional (as deoxycholate): use an antihistamine, paracetamol and/or hydrocortisone in patients who have previously experienced acute adverse reactions to prevent or treat infusion reactions.

» Administration advice (both formulations). Incompatible with sodium chloride solutions, flush existing line with glucose 5% or use a separate line.

» Do not mix with any other drugs.

» After initial reconstitution, do not administer without further dilution.

» Conventional amphotericin B (as deoxycholate) Reduce risk of thrombophlebitis by using large peripheral veins or a CVC, changing venous access sites frequently and infusing over longer periods.

» Reconstitute as per product instructions including further dilution with glucose 5% to produce a final concentration of 0.1 mg/mL (in fluid restricted children up to 0.4 mg/mL if given via a central line).

» Initial test dose should be given over 20–30 minutes. To minimize infusion related reactions, infuse the initial treatment dose slowly over 4–6 hours, tolerance to infusion reactions increases with subsequent doses, which may allow a shorter infusion, however, do not give over < 2 hours.

» Initial test dose should be given over 10 minutes. Then infuse subsequent doses over 30–60 minutes.

» Ensure aseptic technique is maintained in spite of formulation, as mixture does not contain bacteriostatic agents also avoid if there is evidence of foreign precipitate in the bag.

» Amphotericin B is available as deoxycholate, lipid complex and liposomal, these should not be considered interchangeable.

» Care with product formulation. Large overdoses have occurred when conventional formulations were dispensed inadvertently for lipid based or liposomal products. Single daily doses of conventional amphotericin B formulation never exceed 1.5 mg/kg.

» Anaphylaxis has been reported with amphotericin B containing drugs, facilities for cardiopulmonary resuscitation should be available during administration due to the possibility of anaphylactic reaction.

» IV amphotericin B is used primarily for the treatment of patients with progressive fungal infections, not to be used for non-invasive forms of fungal disease.

Clotrimazole

ATC code: G01AF02

Vaginal tablet, 500 mg, LOU 2

Indications and dose

Adult

Vaginal candidiasis, vaginal administration (pessary): 500 mg at night as a single dose

Paediatric: Insufficient experience in children and adolescents, therefore its use is not recommended

Contraindications: Irregular or abnormal vaginal bleeding, vaginal ulcers, foul smelling discharge

Precautions: Age <16 or >60 years. Pregnancy and breastfeeding. STD current or recent

More than two vaginal candidiasis in preceding 6 months

Adverse effects: local irritation.

Interactions: Reduces the efficacy of other antifungals

Notes: Damages latex condoms and diaphragms (advise patients to use alternative contraceptive precautions for at least 5 days after clotrimazole use).

Fluconazole

ATC code: J02AC01

Capsule/tablet, 150 mg, LOU 2

Capsule/tablet, 200 mg, LOU 4

Injection, 2 mg/mL in 100-mL bottle, LOU 4

Oral liquid, 50 mg/5 mL, LOU 4

Indications and dose

Mucosal candidiasis, systemic candidiasis, acute cryptococcal meningitis, genital candidiasis, dermatomycosis, and prophylaxis for chemotherapy and radiotherapy patients

Adult

Systemic mycoses, oral or *By IV infusion:* Initial dose 800 mg, then maintenance at 400 mg until 2 weeks after negative blood cultures (200 mg daily for at least 6 months)

Cryptococcal meningitis (following amphotericin B induction therapy), oral or by IV infusion: 800 mg daily for 2 weeks, followed by 400 mg daily for 8 weeks

Prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy: oral, 200 mg daily or by IV infusion, 100–200 mg daily

Esophageal and oropharyngeal candidiasis, oral or by IV infusion: 200 mg as an initial dose, then 100 mg daily until symptoms resolved, up to 400 mg daily in very resistant infections for 2–4 weeks

Vaginal candidiasis, oral: 150 mg as a single dose

Prevention of fungal infections in immunocompromised patients, oral or by IV infusion: 100–200 mg daily adjusted according to risk; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count is in desirable range; in HIV patients continue indefinitely

Paediatric

Systemic mycoses, oral or IV

Child over 2 years: 3–6 mg/kg (maximum 200 mg) daily for at least 6 months

Cryptococcal meningitis following amphotericin B induction therapy or systemic candidiasis (in patients unable to tolerate amphotericin B), oral or IV

Neonate under 2 weeks: 6–12 mg/kg every 72 hours

Neonate 2–4 weeks: 6–12 mg/kg every 48 hours

Infant or **child:** 6–12 mg/kg (maximum 800 mg) daily

Treatment should continue according to response and should be for at least 8 weeks for cryptococcal meningitis.

Prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy, oral or IV

Infant or **child:** 6 mg/kg (maximum 200 mg) daily

Mucosal candidiasis (except genital), oral or IV

Neonate under 2 weeks: 6–12 mg/kg every 72 hours

Neonate 2–4 weeks: 6–12 mg/kg every 48 hours (must not be exceeded)

Infant or **child:** 3–6 mg/kg on the first day, then 3 mg/kg daily (maximum 100 mg) for 7–14 days

Note: Other mucosal infections, such as oesophagitis, candiduria, and non-invasive bronchopulmonary infections: Treat for 14–30 days

Vaginal candidiasis, oral

Child post-puberty: 150 mg as a single dose

Prevention of fungal infections in immunocompromised patients, oral or IV

Neonate under 2 weeks: 3–12 mg/kg every 72 hours according to duration and extent of neutropenia

Neonate 2–4 weeks: 3–12 mg/kg every 48 hours according to duration and extent of neutropenia.

Infant or **child:** 3–12 mg/kg (maximum 400 mg) daily according to duration and extent of neutropenia

Commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range.

Contraindications: Acute porphyria.

Precautions: Renal impairment, monitor liver function: discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis), concomitant hepatotoxic drugs, susceptibility to QT interval prolongation, patients with proarrhythmic conditions.

Renal impairment: Reduce dose in mild to severe impairment by 50%.

Hepatic impairment: Use with caution.

Adverse effects: Common: Rash, headache, nausea, vomiting, abdominal pain, diarrhoea, elevated liver enzymes.

Anorexia, fatigue, dizziness, constipation.

Rare Oliguria, hypokalaemia, seizures, paraesthesia, alopecia, SJS, toxic epidermal necrolysis (severe skin reactions more common in patients with AIDS), prolonged QT interval, torsades de pointes, thrombocytopenia, other blood dyscrasias, serious hepatotoxicity including hepatic failure, angioedema, anaphylactic/anaphylactoid reactions.

Interactions with other medicines (*indicates serious):

Fluconazole can cause prolonged QT interval and torsades de pointes, avoid concomitant use of other cardiotoxic or arrhythmogenic drugs.

Amphotericin B: possible antagonism of effect of amphotericin.

Artemether + lumefantrine: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

Carbamazepine: fluconazole may inhibit metabolism of carbamazepine and may increase concentration and risk of adverse effects, monitor carbamazepine concentration and for adverse effects.

Ciclosporin: metabolism of ciclosporin inhibited (increased plasma concentration).

Contraceptives, oral: anecdotal reports of failure of estrogen containing contraceptives.

Diazepam: fluconazole may inhibit diazepam's metabolism, increasing the risk of adverse effects.

Ibuprofen: fluconazole may inhibit ibuprofen's metabolism, increasing its concentration and may increase risk of adverse effects.

Nevirapine: increased plasma concentration of nevirapine.

Phenytoin: plasma concentration of phenytoin increased (consider reducing dose of phenytoin).

Rifampicin: accelerated metabolism of fluconazole (reduced plasma concentration).

Ritonavir: plasma concentration of fluconazole increased by ritonavir.

Saquinavir: plasma concentration of saquinavir possibly increased.

Warfarin: enhanced anticoagulant effect.

Notes:

- For IV infusion, give over 60 minutes at a maximum rate of 200 mg/hour. Higher doses are best infused over 2 hours.
- Food decreases the rate but not the extent of absorption. Bioavailability is excellent at > 90%.
- Fluconazole oral liquid may contain sodium benzoate and should be used with caution in neonates

Flucytosine

ATC code: J02AX01

Injection, 2.5g/250ml

Capsule, 250 mg, LOU 4

Indications and dose

Adult

Adjunct to amphotericin B (or fluconazole) in cryptococcal meningitis, adjunct to amphotericin B in systemic candidiasis, systemic candidiasis, and cryptococcosis, by IV infusion 200mg/kg daily in four divided doses not more than seven days or 100mg -150 mg/kg daily in four divided doses

oral: 50–150 mg/kg daily in 4 divided doses

Paediatric

Adjunct to amphotericin B (or fluconazole) in cryptococcal meningitis, adjunct to amphotericin-B in systemic candidiasis, by IV Infusion:

Neonate: 50mg/kg every 12 hours

Child: 50 mg/kg every 6 hours usually for not more than 7 days, alternatively 25–37.5 mg/kg every 6 hours usually for not more than 7 days

Oral:

Child: 50 mg/kg every 6 hours. In infections due to extremely sensitive organisms, 25–37.5 mg/kg every 6 hours may be sufficient. Treatment does not usually extend beyond 7 days. Continue for at least 4 months in cryptococcal meningitis.

Precautions: Renal impairment, use with amphotericin B (both nephrotoxic), hepatic impairment, liver and kidney function tests and blood counts required (weekly in renal impairment or in blood disorders), bone marrow depression, myelosuppressive drugs, radiation treatment, patients with AIDS have an increased risk of blood dyscrasias, monotherapy due to emergent resistance.

Renal impairment: Reduce dose and monitor plasma flucytosine concentration.

- Mild renal impairment: usual dose every 12 hours.
- Moderate renal impairment: usual dose every 24 hours.
- Severe renal impairment: usual dose every 24–48 hours.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common: Nausea, vomiting, diarrhoea, rashes, thrombocytopenia, photosensitivity. Frequency unknown: Cardiotoxicity, confusion, hallucinations, psychosis, seizures, headache, sedation, vertigo, GI haemorrhage, alterations in liver function tests including hepatitis, toxic epidermal necrolysis, peripheral neuropathy.

Rare: Anaphylaxis, hepatic necrosis, blood disorders including thrombocytopenia, leukopenia and aplastic anaemia.

Interactions with other medicines (*indicates serious):

Flucytosine depresses the bone marrow, administration with other drugs which also have this effect may increase the risk of myelosuppression.

If it is given with nephrotoxic drugs, its renal excretion may be reduced, increasing the risk of toxicity.

Amphotericin B: renal excretion of flucytosine decreased and cellular uptake increased (flucytosine toxicity possibly increased).

Cytarabine: plasma flucytosine concentration possibly reduced.

Zidovudine: concomitant administration may increase the risk of haematological toxicity. Caution if used together.

Notes:

- Monitoring is essential in renal impairment, when using with amphotericin B, or if there is an increased risk of bone marrow suppression, e.g., in patients with AIDS.
- Resistance to flucytosine can develop during therapy and sensitivity testing is essential before and during treatment.
- The capsules are taken with food to reduce stomach upset.
- For plasma concentration monitoring, blood should be taken shortly before starting the next infusion (or before next dose oral). Plasma concentration for optimum response 25–50 mg/L (200–400 micromol/L) and should not exceed 80 mg/L (620 micromol/L).

Griseofulvin

ATC code: D01BA01

Tablet, 125 mg, 500 mg, LOU 2

Indications and dose

Adult

Superficial fungal infections, oral: 0.5–1 g (but not less than 10 mg/kg) daily with fatty food in single or divided doses

Duration of treatment depends on the infection and thickness of keratin at the site of infection: at least

4 weeks for skin and hair, at least 6 weeks for scalp ringworm (and in severe infection, up to 3 months), up to 6 months for fingernails, and up to 12 months or more for toenails.

Paediatric

Fungal infections of the skin, scalp or hair where topical treatment has failed or is inappropriate, oral

Infant or **child:** 10–20 mg/kg (maximum 1 g) once daily or in divided doses, use divided doses if treatment is failing; up to 25 mg/kg/day for 6–8 weeks may be required for the treatment of tinea capitis

Duration of treatment depends on the infection and thickness of keratin at site of infection. As a guide:

2–4 weeks: Tinea corporis

4–8 weeks: Tinea pedis and tinea capitis

6–12 weeks: Tinea ungium

Contraindications: Severe liver disease, pregnancy (avoid pregnancy and use additional non-oral contraception during and for 1 month after treatment, men should not father children within 6 months of treatment), porphyria, SLE (risk of exacerbation).

Precautions: Avoid exposure to intense sunlight to prevent photosensitivity reactions, penicillin hypersensitivity (cross-reactivity with griseofulvin is possible), pre-existing hepatic insufficiency (closely monitor hepatic function throughout treatment), blood disorders (monitor blood count weekly during first month of treatment).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Contraindicated in severe liver disease.

Adverse effects: Common: Headache, nausea, diarrhoea, anorexia. Uncommon: Photosensitivity, urticaria, rash, blurred vision, confusion, fatigue, dizziness, taste disturbance. Rare: Precipitation/exacerbation of SLE, vomiting, severe diarrhoea, menstrual irregularities, leukopenia, hepatotoxicity, hypersensitivity, e.g., serum sickness-like reaction, SJS, toxic epidermal necrolysis.

Interactions with other medicines (*indicates serious):

Ciclosporin: plasma ciclosporin concentration possibly reduced.

Contraceptives, oral: accelerated metabolism of estrogens and progestogens (reduced contraceptive effect).

Ethanol: disulfiram-like reaction (nausea, vomiting, diarrhoea, flushing, tachycardia, hypotension).

Levonorgestrel: accelerated metabolism of levonorgestrel (reduced contraceptive effect).

Medroxyprogesterone: accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception).

Norethisterone: accelerated metabolism of norethisterone (reduced contraceptive effect).

Phenobarbital: reduction in absorption of griseofulvin (reduced effect).

Warfarin: reduced anticoagulant effect.

Notes:

- Fatty meals will increase griseofulvin absorption. Administer with a fatty meal or with food or milk to improve absorption and to avoid GI upset.
- Patient advice Avoid consumption of alcoholic beverages during treatment with griseofulvin.
- Avoid sun exposure, wear protective clothing and use sunscreen as griseofulvin may make you more sensitive to sunlight.
- The contraceptive pill will not be as effective while you are taking griseofulvin, you should use additional contraception, e.g., condoms, during treatment and for 4 weeks afterwards.
- Griseofulvin also carries a high teratogenic risk and hence is to be avoided in pregnancy.
- Skilled tasks: Warn patient or caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Itraconazole

ATC code: J02AC02

Capsule, 100 mg, LOU 5

Indications and dose

Adult

Oropharyngeal candidiasis, oral: 100 mg (or 200 mg in patients with aids or neutropenia) daily for 15 days

Vulvovaginal candidiasis, oral: 200 mg twice daily for 1 day

Pityriasis versicolor, oral: 200 mg daily for 7 days

Dermatophytosis, oral: 100 mg daily for 15 days or 200 mg daily for 7 days in tinea corporis or tinea cruris; doses are 100 mg daily for 30 days or 200 mg twice daily for 7 days in tinea pedis or tinea manuum

Nail infections, oral: 200 mg daily for 3 months or pulse therapy with 200 mg twice daily for 7 days repeated once (for fingernails) or twice (for toenails) after drug free intervals of 21 days

Systemic infections, oral: Given in usual doses of 100 to 200 mg once daily, increased to 200 mg twice daily for invasive or disseminated infections, including cryptococcal meningitis

Paediatric

Oropharyngeal candidiasis, oral

Child up to 11 years: 3–5 mg/kg once daily for 15 days, maximum 100 mg per day

Child 12–17 years: 100 mg once daily for 15 days

Oropharyngeal candidiasis in patients with AIDS or neutropenia, oral

Child up to 11 years: 3–5 mg/kg once daily for 15 days, maximum 200 mg per day

Child 12–17 years: 200 mg once daily for 15 days

Systemic candidiasis where other antifungal drugs inappropriate or ineffective, oral

5 mg/kg once daily (max. per dose 200 mg); dose increased in invasive or disseminated disease and in cryptococcal meningitis, increased to 5 mg/kg twice daily (max. per dose 200 mg)

Pityriasis versicolor, oral

Child 1 month–11 years: 3–5 mg/kg once daily (max. per dose 200 mg) for 7 days

Child 12–17 years: 200 mg once daily for 7 days

Tinea pedis, Tinea manuum, oral

Child 1 month–11 years: 3–5 mg/kg once daily (max. per dose 100 mg) for 30 days

Child 12–17 years: 100 mg once daily for 30 days, alternatively 200 mg twice daily for 7 days

Tinea corporis, Tinea cruris, oral

Child 1 month–11 years: 3–5 mg/kg once daily (max. per dose 100 mg) for 15 days

Child 12–17 years: 100 mg once daily for 15 days, alternatively 200 mg once daily for 7 days

Tinea capitis, oral

Child 1–17 years: 3–5 mg/kg once daily (max. per dose 200 mg) for 2–6 weeks

Onychomycosis, oral

Child 1–11 years: 5 mg/kg daily (max. per dose 200 mg) for 7 days, subsequent courses repeated after 21-day intervals, fingernails 2 courses, toenails 3 courses

Child 12–17 years: 200 mg once daily for 3 months, alternatively 200 mg twice daily for 7 days, subsequent courses repeated after 21-day intervals, fingernails 2 courses, toenails 3 courses

Systemic aspergillosis where other antifungal drugs inappropriate or ineffective, oral

Child: 5 mg/kg once daily (max. per dose 200 mg), increased to 5 mg/kg twice daily (max. per dose 200 mg), dose increased in invasive or disseminated disease and in cryptococcal meningitis

Histoplasmosis, oral

Child: 5 mg/kg 1–2 times a day (max. per dose 200 mg)

Systemic cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective, oral

Child: 5 mg/kg once daily (max. per dose 200 mg), dose increased in invasive or disseminated disease and in cryptococcal meningitis, increased to 5 mg/kg twice daily (max. per dose 200 mg)

Maintenance in HIV-infected patients to prevent relapse of underlying fungal infection and prophylaxis in neutropenia when standard therapy inappropriate, oral

Child: 5 mg/kg once daily (max. per dose 200 mg), then increased to 5 mg/kg twice daily (max. per dose 200 mg), dose increased only if low plasma itraconazole concentration

Prophylaxis of deep fungal infections (when standard therapy inappropriate) in patients with haematological malignancy or undergoing bone-marrow transplantation who are expected to become neutropenic, oral

Child: 2.5 mg/kg twice daily, to be started before transplantation or before chemotherapy (taking care to avoid interaction with cytotoxic drugs) and continued until neutrophil count recovers; safety and efficacy not established

Contraindications: Acute porphyrias

Precautions: Active liver disease, history of hepatotoxisity with other drugs, susceptibility to congestive heart failure:

» **Heart Failure:** Increased incidences of decreased left ventricular ejection fraction with Itraconazole, consider alternatives in patients with heart failure or those on concomitant use of CCBs.

Reduced Gastric acidity

Patients with achlorhydria or taking acid suppressing medication, will have lower overall bioavailabilty due to decreased absorption

Hepatic impairment: Manufacturer advises use only in serious or life-saving situations where potential benefit outweighs risk of hepatotoxicity.

Renal impairment: Risk of congestive heart failure. Bioavailability of oral formulations possibly reduced.

Conception and contraception: Ensure effective contraception during treatment and until the next menstrual period following end of treatment.

Pregnancy: Manufacturer advises use only in life-threatening situations (toxicity at high doses in animal studies).

Breastfeeding: Small amounts present in milk—may accumulate, manufacturer advises avoid.

Adverse Effects: Common: dyspepsia, abdominal pain, nausea, vomiting, constipation, diarrhoea, headache, and dizziness. Others include: allergic reactions such as pruritus, rash, urticaria, angioedema, and photosensitivity. Isolated cases of SJS, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, and leucocytoclastic vasculitis have also been associated with itraconazole.

An increase in liver enzyme values has occurred in some patients and cases of hepatitis and cholestatic jaundice have been seen, especially in those treated for more than one month. There have been rare cases of liver failure and death. Heart failure and pulmonary oedema have been reported rarely and serious cardiovascular events including arrhythmias and sudden death have been attributed to Interactions with other medicines in patients receiving itraconazole. Incidence of adverse drug reactions is much higher in the paediatric population

Notes: Monitoring requirements:

» Absorption reduced in AIDS and neutropenia

(monitor plasma-itraconazole concentration and increase dose if necessary).

» Monitor liver function if treatment continues for longer than one month, if receiving other hepatotoxic drugs, or if history of hepatotoxicity with other drugs.

Nystatin

ATC code: A07AA02

Oral liquid (suspension), 100 000 IU/mL, LOU 2

Indications and dose

Adult

Oral candidiasis, oral: 100,000 units after food four times daily usually for 7 days, continue for 48 hours after lesions have resolved

Intestinal and esophageal candidiasis, oral: 500,000 units four times daily, continue for 48 hours after clinical cure

Paediatric

Oral candidiasis, oral

Child over 1 month: 100,000 units four times daily after feeds; treatment is usually given for 7 days and continued for 2 days after lesions have healed.

Intestinal and esophageal candidiasis, oral

Child over 1 month: 100,000 units four times daily after feeds; immunocompromised children may require 500,000 units four times daily

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary

Adverse effects: Common: Nausea, vomiting, diarrhoea (more severe with doses > 5 million units daily). Rare: Oral irritation and sensitization, rash and erythema multiforme (SJS).

Interactions with other medicines: There are no known interactions where it is recommended to avoid concomitant use.

Notes:

» Each mg of nystatin contains not less than 4400 units of activity.

» Patient advice: For oral liquid shake well before use. It is best to use the oral liquid after (rather than before) a meal or drink. Should be swished around the mouth and retained for as long as possible then swallowed.

» Continue to use for 2 days after your symptoms/ lesions disappear.

Posaconazole

ATC code: J02AC04

Injection, 18mg/mL (300mg/16.7ml), LOU 6

Tablet (Delayed release), 100 mg, LOU 6

Indications and dose

Adult

Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products, fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B, Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole, coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products: Loading dose 300mg (three 100mg tablets) twice daily on the first day, switch from intravenous to oral when appropriate.

Prophylaxis of invasive fungal infections in patients at high risk and undergoing high-dose immunosuppressive therapy for hematopoietic stem cell transplantation or receiving chemotherapy for acute myeloid leukemia or myelodysplastic syndrome and expected to develop prolonged neutropenia; Loading dose 300 mg twice daily on first day, then 300 mg once daily, for chemotherapy patients, start several days before the expected onset of neutropenia and continue for 7 days after neutrophil count rises above 500 cells/mm3, switch from intravenous to oral route when appropriate.

Contraindications: Co-administration with ergot alkaloids. Co-administration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine (may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes). Co-administration with HMG-CoA reductase inhibitors simvastatin, lovastatin and atorvastatin. Co-administration during the initiation and dose-titration phase of venetoclax in Chronic Lymphocytic Leukaemia (CLL) patients.

Precautions: Caution should be used when prescribing posaconazole to patients with hypersensitivity to other azoles. used with caution in patients with hepatic impairment (Discontinuation of posaconazole should be considered if clinical signs and symptoms are consistent with development of liver disease). administered with caution to patients with pro-arrhythmic conditions such as congenital or acquired QTc prolongation, cardiomyopathy, especially in the presence of cardiac failure, sinus bradycardia, existing symptomatic arrhythmias, concomitant use with medicinal products known to prolong the QTc interval. Posaconazole is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolised by CYP3A4.

Hepatic impairment: Use with caution due to the potential for higher plasma exposure

Renal impairment: no dose adjustment is recommended

Pregnancy: Posaconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk

Breastfeeding: Breast-feeding must be stopped on initiation of treatment with posaconazole

Adverse effects: neutropenia, electrolyte imbalance, anorexia, decreased appetite, hypokalaemia, hypomagnesaemia, paraesthesia, dizziness, somnolence, headache, dysgeusia, hypertension, nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, constipation, anorectal discomfort, liver function tests raised, rash, pruritis, fever, asthenia, fatigue.

Interactions with other medicines: verapamil, ciclosporin, quinidine, clarithromycin, erythromycin, rifampicin, rifabutin, phenytoin, efavirenz, Fosamprenavir, tacrolimus, sirolimus, atazanavir, midazolam, Terfenadine, astemizole, cisapride, pimozide, halofantrine and quinidine.

Terbinafine

ATC code: D01BA02

Tablet, 125 mg, 250 mg, LOU 4

Indications and dose

Adult

Dermatophytes, onchomycosis, oral: 250 mg is given once daily for 2 to 4 weeks for tinea cruris; treatment may be continued for up to 6 weeks for tinea pedis infections; a 4-week course is used in tinea corporis infections.

Note: Dermatophyte infections of the nails are treated with the equivalent of terbinafine 250 mg orally once daily for 6 to 12 weeks; longer treatment may be necessary in toenail infections.

Paediatric

Treatment of dermatophyte infections of the skin and nails in children over 1 year of age, oral

Weighing 10 to 20 kg: Equivalent of terbinafine 62.5 mg once daily

Weighing 20 to 40 kg: 1 2 5 mg once daily

Weighing over 40 kg: 250 mg once daily

Treatment is usually given for 4 weeks for tinea capitis, 2 to 4 weeks for tinea cruris, 4 weeks for tinea corporis, and may be continued for up to 6 weeks in tinea pedis. Infections of the nails are treated for 6 weeks to 3 months; longer treatment may occasionally be required for toenail infections.

Precautions: With oral use psoriasis (risk of exacerbation), risk of SLE

Hepatic impairment: With oral use manufacturer advises avoid (risk of increased exposure). Preferable to conduct liver function tests before initiation.

Renal impairment: Dose adjustments - Use half normal dose if eGFR less than 50 mL/min/1.73 m2 or Serum creatinine of more than 300 mmol/L and no suitable alternative available.

Pregnancy: use only if potential benefit outweighs risk—no information available.

Breastfeeding: Avoid—present in milk.

Adverse effects: Common or very common: Skin reactions, Appetite decreased, arthralgia, diarrhoea, GI discomfort, GI disorder, Headache, myalgia, nausea. Uncommon: Taste altered. Rare or very rare: Agranulocytosis, alopecia, cutaneous lupus erythematosus, dizziness, hepatic disorders, malaise, neutropenia, photosensitivity reaction, sensation abnormal, SCARs, SLE, thrombocytopenia, vertigo. Frequency not known: Anaemia, anxiety, depressive symptom, fatigue, fever, hearing impairment, influenza like illness, pancreatitis, pancytopenia, rhabdomyolysis, serum sickness-like reaction, smell altered, tinnitus, vasculitis, vision disorders. Hepatic toxicity with oral use: discontinue treatment if liver toxicity develops (including jaundice, cholestasis and hepatitis). Serious skin reactions with oral use: discontinue treatment in progressive skin rash (including SJS and toxic epidermal necrolysis).

Notes: Monitoring requirements: With oral use: Monitor hepatic function before treatment and then periodically after 4–6 weeks of treatment—discontinue if abnormalities in liver function tests.

Voriconazole

ATC code: J02AC03

Powder for injection, 200-mg vial, LOU 5

Tablet: 200mg LOU 5

Indications and dose

Adult

Invasive aspergillosis, serious infections caused by Scedosporium spp., Fusarium spp., invasive fluconazole-resistant Candida spp. (including C. krusei), and prophylaxis in the immunosuppressed but not more than 6 months, by IV infusion: Initially 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours, reduced if not tolerated to 3 mg/kg every 12 hours, for max. 6 months

Oral: For body weight up to 40kg: 200mg every 12 hours for two doses, then 100mg every 12 hours, increases if necessary to 150mg every 12 hours. For body weight 40kg and above: initially 400mg every 12 hours for two doses, then 200mg every 12 hours, increased if needed to 300mg every 12 hours

Paediatric

Treatment of invasive aspergillosis, candidemia in non-neutropenic patients, serious fluconazole-resistant invasive candidiasis, serious infections caused by Scedosporium or Fusarium spp., and prophylaxis in immunosuppressed patients no more than 6 months, by Iv infusion

Child 2 years to 14 years weighing <40 kg: Treat with IV voriconazole initially and then switch to oral treatment only if clinically appropriate. The following doses are suggested:

IV: Loading dose of 9 mg/kg twice daily for the first 24 hours, followed by a maintenance dose of 8 mg/kg twice daily; infusion rate should not exceed 3 mg/kg per hour

Oral:

Child 2–11 years; maintenance 9 mg/kg every 12 hours, adjusted in steps of 1 mg/kg and increased if necessary up to 350 mg every 12 hours, then adjusted in steps of 50 mg as required

Child 12–14 years (body-weight up to 50 kg); maintenance 9 mg/kg every 12 hours, adjusted in steps of 1 mg/kg and increased if necessary up to 350 mg every 12 hours, then adjusted in steps of 50 mg as required.

Note: Treatment should be initiated with intravenous regimen, and oral regimen should be considered only after there is a significant clinical improvement

Child 12–14 years (body-weight 50 kg and above): Initially 400 mg every 12 hours for 2 doses, then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours

Child 15–17 years (body-weight up to 40 kg): Initially 200 mg every 12 hours for 2 doses, then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours

Child 15–17 years (body-weight 40 kg and above): Initially 400 mg every 12 hours for 2 doses, then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours

Contraindications: Acute porphyria. **Co-administration:** Concomitant use with carbamazepine, rifampicin, ritonavir or long-acting barbiturates is contraindicated – phenobarbital. Phenytoin, efavirenz and fluconazole can be co-administered with dose adjustments.

Precautions: Avoid exposure to sunlight, bradycardia, cardiomyopathy, electrolyte, disturbances, history of QT, interval prolongation, patients at risk of pancreatitis, symptomatic arrhythmias

Hepatic impairment: Manufacturer advises caution, particularly in severe impairment (no information available). Dose adjustments Manufacturer advises use usual initial loading dose then halve maintenance dose in mild to moderate cirrhosis.

Renal impairment: IV vehicle may accumulate if eGFR less than 50 mL/min/1.73 m2— use IV infusion only if potential benefit outweighs risk, and monitor renal function,

Conception and contraception: Effective contraception required during treatment.

Pregnancy: Toxicity in animal studies—manufacturer advises avoid unless potential benefit outweighs risk.

Breastfeeding: avoid—no information available

Adverse effects: Common or very common: Acute kidney injury, agranulocytosis, alopecia, anaemia, anxiety, arrhythmias, asthenia, bone marrow disorders, chest pain, chills, confusion, constipation, depression, diarrhoea, dizziness, drowsiness, dyspnoea, electrolyte imbalance, eye disorders, eye inflammation, fever, GI discomfort, haemorrhage, hallucination, headache, hepatic disorders, hypoglycaemia, hypotension, increased risk of infection, insomnia, leucopenia, muscle tone increased, nausea, neutropenia, oedema, oral disorders, pain, pulmonary oedema, respiratory disorders, seizure, sensation abnormal, skin reactions, syncope, tetany, thrombocytopenia, tremor, vision disorders, vomiting. Uncommon: Adrenal insufficiency, arthritis, brain oedema, duodenitis, encephalopathy, eosinophilia, gallbladder disorders, hearing impairment, hypothyroidism, influenza like illness, lymphadenopathy, lymphangitis, movement disorders, nephritis, nerve disorders, pancreatitis, parkinsonism, phototoxicity, proteinuria, pseudomembranous enterocolitis, QT interval prolongation, renal tubular necrosis, SCARs, taste altered, thrombophlebitis, tinnitus, vertigo. Rare or very rare: Angioedema, cardiac conduction disorders, disseminated intravascular coagulation, hyperthyroidism. Frequency not known: Cutaneous lupus erythematosus, periostitis (more common in transplant patients), squamous cell carcinoma (more common in presence of phototoxicity). Specifically with IV use: infusion related reaction. **Hepatotoxicity:** Hepatitis, cholestasis, and acute hepatic failure have been reported,

risk of hepatotoxicity increased in patients with haematological malignancy.

Consider treatment discontinuation if severe abnormalities in liver function tests. **Phototoxicity**: Phototoxicity occurs rarely but photoprotective clothing and sun protection factor (SPF) > 30 for duration of treatment is recommended. If phototoxicity occurs, consider treatment discontinuation, if treatment is continued, monitor for pre-malignant skin lesions and squamous cell carcinoma, and discontinue treatment if they occur.

Notes:

Monitoring requirements: Monitor renal function. Monitor liver function before starting treatment, then at least weekly for 1 month, and then monthly for duration of treatment.

Dose adjustments due to interactions: With IV use manufacturer advises increasing the maintenance dose to 5 mg/kg every 12 hours with concurrent use of fosphenytoin, phenytoin or rifabutin.

Directions for administration: For IV infusion, reconstitute each mL with 19 mL water for injection or sodium chloride 0.9% to produce a 10 mg/mL solution, dilute dose to concentration of 0.5–5 mg/mL with glucose 5% or sodium chloride 0.9% and give intermittently

Notes: Monitoring requirements: With oral use: Monitor hepatic function before treatment and then periodically after 4–6 weeks of treatment—discontinue if abnormalities in liver function tests.

7.4. Antiviral Medicines

7.4.1. Antiherpes Medicines

Acyclovir (Aciclovir)

ATC code: J05AB01

Powder for injection, 250 mg (as sodium salt) in vial, LOU 4

Tablet (scored), 400 mg, LOU 2

Indications and dose

Adult

Herpes simplex (including genital herpes), oral: 200 mg (400 mg in the immunocompromised or if absorption is impaired) 5 times daily, usually for 5 days (longer if new lesions appear during treatment or if healing is incomplete)

Herpes simplex in the immunocompromised, severe initial genital herpes, by IV infusion: 5 mg/kg every 8 hours, usually for 5 days.

Prevention of recurrent herpes simplex, oral: 200 mg 4 times daily or 400 mg twice daily, reduced to 200 mg 2–3 times daily if possible and interrupted every 6–12 months for reassessment.

Prophylaxis of herpes simplex in the

immunocompromised, oral: 200–400 mg 4 times daily

Chickenpox, oral: 800 mg 4–5 times daily for 5–7 days

Herpes zoster, oral: 800 mg 5 times daily for 7–10 days

Varicella-zoster, by IV infusion: 5 mg/kg every 8 hours, usually for 5–7 days (doubled in the immunocompromised)

Herpes simplex encephalitis, varicella-zoster in the immunocompromised, by IV infusion: 10 mg/kg every 8 hours, usually given for at least 10 days in encephalitis, possibly for 14–21 days

Paediatric

Herpes simplex (non-encephalitis) treatment including genital herpes

Immunocompetent patients, oral

Child less than 2 years: 100 mg five times daily

Child 2 years and over: 200 mg five times daily

Treatment usually for 5 days, longer if new lesions appear during treatment or if healing

incomplete.

Herpes simplex in the Immunocompromised patients, oral

Child 1 month–2 years: 200 mg five times daily for 7–14 days

Child 2–12 years: 400 mg five times daily for 7–14 days

Disseminated herpes simplex treatment, IV infusion

Neonate to **infant under 3 months**: 20 mg/kg every 8 hours for 10–14 days (21 days if CNS involved)

Child 3 months–12 years: 250 mg/m2 every 8 hours, usually for 5 days

Herpes simplex prophylaxis in immunocompromised patients, oral

Child less than 2 years: 100–200 mg four times daily

Child 2 years and over: 200–400 mg four times daily

Chickenpox (usually only prescribed if immunocompromised), oral

Child less than 2 years: 200 mg four times daily

Child 2–5 years: 400 mg four times daily

Child over 5 years: 800 mg four times daily

Varicella zoster treatment

Immunocompetent patients, IV infusion

Neonate to **infant under 3 months:** 10–20 mg/kg every 8 hours for at least 7 days

Child 3 months–12 years: 250 mg/m2 every 8 hours usually for 5 days

Immunocompromised patients, IV infusion

Neonate to **infant under 3 months:** 20 mg/kg every 8 hours for at least 7 days

Child 3 months–12 years: 500 mg/m2 every 8 hours usually for 5 days

Herpes simplex encephalitis, IV infusion

Child 3 months–12 years: 500 mg/m2 every 8 hours usually for 14–21 days **Precautions:** Maintain adequate hydration, renal impairment.

Renal impairment: IV dose reduction required in mild to severe impairment.

Oral dose reduction required in moderate to severe impairment.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common: Nausea, vomiting, diarrhoea, hallucinations (high dose), headache, encephalopathy (reported in 1% patients with IV use), injection site reactions. Uncommon: With IV use: Anaemia, leucopenia, thrombocytopenia. Rare: Agitation, vertigo, confusion, dizziness, oedema, renal impairment, arthralgia, sore throat, abdominal pain, constipation, rash, weakness. Coma, seizures, neutropenia, leukopenia, anaemia, thrombocytopenia, crystalluria, *anorexia*, fatigue, hepatitis, SJS, toxic epidermal necrolysis, anaphylaxis.

Interactions with other medicines (*indicates serious):

Ciclosporin: increased risk of nephrotoxicity.

Zidovudine: neurotoxicity.

Notes:

- Make sure that you drink plenty of fluids.
- If you wish, you can disperse tablets in water.

7.4.2. Antiretrovirals

Essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post-exposure prophylaxis); using FDC medicines for ART is recommended. Users of the KNMF are advised to refer to updated national treatment guidelines.

7.4.2.1. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

Abacavir (ABC)

ATC code: J05AF06

Tablet, 300 mg (as sulphate), LOU 2

Oral solution, 20 mg/ml

Indications and dose

Adult

HIV infection, in combination with at least two other antiretroviral medicines: 300 mg twice daily

Paediatric

HIV infection, in combination with other antiretroviral drugs, oral

Infant or **child:** 8 mg/kg/dose given twice daily, maximum 300 mg twice daily

Abacavir: Recommended dosing using 300-mg tablets according to weight bands

Weight range (kg) <16 years or <37.5 kg: 8 mg/kg/dose given twice daily Maximum dose >16 years or ≥37.5 kg: 300 mg/dose given twice daily		Target dose	Dose (tablets)	
minimum (Kg)	minimum (Kg)	Formulation	a.m.	p.m.
25	29.9	300-mg tablet	1	1
30	34.9	300-mg tablet	1	1

Abacavir: Recommended dosing using oral liquid and 300-mg tablets according to weight bands

Weight range (kg) <16 years or <37.5 kg: 8 mg/kg/dose given twice daily Maximum dose >16 years or ≥37.5 kg: 300 mg/dose given twice daily		Target dose	Dose (mL or tablets)	
minimum (Kg)	maximum (Kg)	Formulation	a.m.	p.m.
3	3.9	Oral solution	3 mL	3 mL
4	4.9	Oral solution	3 mL	3 mL
5	5.9	Oral solution	3 mL	3 mL
6	6.9	Oral solution	4 mL	4 mL
7	7.9	Oral solution	4 mL	4 mL
8	8.9	Oral solution	4 mL	4 mL
9	9.9	Oral solution	4 mL	4 mL
10	10.9	Oral solution	6 mL	6 mL
11	11.9	Oral solution	6 mL	6 mL
12	13.9	Oral solution	6 mL	6 mL
14	16.9	300-mg tablet	0.5	0.5
17	19.9	300-mg tablet	0.5	0.5
20	24.9	300-mg tablet	1	0.5
25	29.9	300-mg tablet	1	1
30	34.9	300-mg tablet	1	1

Contraindications: Severe renal impairment, severe hepatic impairment, previous hypersensitivity reaction to abacavir.

Precautions: Chronic hepatitis B or C, hepatic impairment, renal impairment.

Renal impairment: Severe: avoid.

Hepatic impairment: Moderate: avoid unless essential. Severe: avoid.

Adverse effects: Common: Nausea, vomiting, fever, headache, diarrhoea, rash, anorexia, fatigue. Rare or very rare: Lactic acidosis, severe hepatomegaly with steatosis, pancreatitis, hypersensitivity, lipodystrophy (see below). Increased liver enzymes, elevated blood glucose, elevated triglycerides, possible increased risk of MI.

Lipodystrophy: has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established. **Hypersensitivity reactions:** Life-threatening hypersensitivity reactions characterized by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, dyspnoea, cough, lethargy, malaise, headache and myalgia, less frequently oral ulceration, oedema, hypotension, sore throat, adult respiratory distress syndrome, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia, renal failure and anaphylaxis (hypersensitivity reactions presenting as sore throat, influenza-like illness, cough and breathlessness identified), and rarely by myolysis. Laboratory abnormalities may include raised liver enzymes (see below) and creatine kinase. Symptoms usually appear in the first 6 weeks, but may occur at any time, monitor patients for symptoms every 2 weeks for 2 months, discontinue immediately if any symptom of hypersensitivity develops and do not rechallenge (risk of more severe hypersensitivity reaction), discontinue if hypersensitivity cannot be ruled out, even when other diagnoses possible (if rechallenge necessary, it must be carried out in hospital setting). If abacavir is stopped for any reason other than hypersensitivity, exclude hypersensitivity reaction as the cause, and rechallenge only if medical assistance is readily available, care needed with concomitant use of drugs which cause skin toxicity. Studies have shown an association between abacavir hypersensitivity and a specific HLA genotype (HLA-B*5701). This genetic screening for HLA-B*5701 is recommended prior to initiation of abacavir based therapy. The incidence of abacavir hypersensitivity reaction is lower in the non-Caucasian population.

Hepatic disease: Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis have been reported. Caution in patients with hepatomegaly, hepatitis, liver enzyme abnormalities, or risk factors for liver disease and hepatic steatosis (including alcohol abuse), discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis.

Interactions with other medicines (*indicates serious):

Methadone: plasma concentration of methadone possibly reduced.

Phenobarbital: plasma concentration of abacavir possibly reduced.

Phenytoin: plasma concentration of abacavir possibly reduced.

Rifampicin: plasma concentration of abacavir possibly reduced.

Notes:

- Patient advice: Patients and caregivers should be told the importance of regular dosing (intermittent therapy may increase sensitization), how to recognize signs of hypersensitivity, and advised to seek immediate medical attention if symptoms develop or before restarting treatment.
- Abacavir should be stopped permanently if hypersensitivity reaction occurs.
- Can be given without regard to food.

- Store oral solution at room temperature (20–25 °C), may be refrigerated.
- Tablets may be crushed with a small amount of water or food and administered immediately.
- Antiretroviral dosing: The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection in infants and children: towards universal access. Recommendations for a public health approach)*. At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.
- The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on BSA may be impractical in resource-limited settings. The target doses for each drug are included in the tables, however in many cases, the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.
- Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.
- Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Lamivudine (3TC)

ATC code: J05AF05

Oral liquid, 10 mg/mL (50 mg/5 mL), LOU 2

Indications and dose

Adult

HIV infection (in combination with other antiretroviral medicines), oral: 150 mg twice daily or 300 mg once daily

Prevention of mother-to-child transmission of HIV: 150 mg at onset of labour followed by 150 mg every 12 hours until delivery; after delivery 150 mg twice a day for 7 days

Paediatric

HIV infection, in combination with other antiretroviral drugs, oral

Neonate: 2 mg/kg/dose given twice daily

Infant or **child:** 4 mg/kg/dose given twice daily, maximum 150 mg twice daily

Contraindications: Hypersensitivity to active substance or any of the excipients

Precautions: Pancreatitis (see below), renal impairment, chronic hepatitis B or C, hepatic disease (see below).

- Pancreatitis: If no suitable alternative exists, use with extreme caution in children with advanced HIV infection, previous history of pancreatitis or risk factors for pancreatitis.
- Hepatic disease: Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported, caution in children with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa and ribavirin), liver enzyme abnormalities, or risk factors for liver disease and hepatic steatosis, discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine.

Renal impairment: Moderate to severe: reduce dose.

Hepatic impairment: Dosage adjustment not required, use with caution in patients with decompensated liver disease. See notes in Precautions.

Adverse effects: Common: Headache, fatigue, nausea, anorexia, diarrhoea, skin rash, abdominal pain, pancreatitis (more commonly reported in children, up to 14%). Rare or very rare: Peripheral neuropathy, anaemia, decreased neutrophil count, increased liver enzymes, fat redistribution (see Lipodystrophy below), lactic acidosis, severe hepatomegaly with steatosis. **Lipodystrophy:** has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (*indicates serious): Emtricitabine: no information available, manufacturer advises to avoid concomitant use.

Interferon alfa: increased risk of hepatic toxicity.

Ribavirin: increased risk of hepatic toxicity.

Sulfamethoxazole + trimethoprim: plasma concentration of lamivudine increased (avoid concomitant use of high dose sulfamethoxazole + trimethoprim).

Notes:

- Can be given without regard to food.
- Store oral solution at room temperature. Use within 1 month of opening.
- Tablets may be crushed with a small amount of water or food and administered immediately.
- Also active against hepatitis B. Patients co-infected with HIV and hepatitis B should receive the HIV doses of lamivudine as above.

Tenofovir Alafenamide (TAF)

ATC code: J05AF13

Tablet , 25 mg, LOU 4

Indications and dose

Adult

HIV/AIDs (prefarably use an FDC antiretroviral medication): 25mg once daily, taken with food (in combination with other antiretroviral agents)

Paediatric

HIV/Aids / specialist advise

Contraindications: Hypersensitivity to tenofovir alafenamide, patients with galactose intolerance

Precautions: Patients with decompensated liver disease, Acute exacerbation of hepatitis b after treatment discontinuation,

Hepatic impairment: Not recommended in severe decompensated liver disease.

Renal impairment: Not recommended in patients with creatinine clearance less than 15ml/min who are not receiving hemodialysis

Pregnancy: Maybe considered if necessary

Breastfeeding: It is unknown whether it is secreted in breast milk

Adverse effects: headache, nausea, fatigue, changes in lipid profile, dizziness, abdominal pain, abdominal distention, flatulence, increased ALT, rash, pruritis, angioedema, arthralgia, fatigue

Interactions with other medicines: Carbamazepine, oxcarbamazepine, phenytoin, phenobarbitone, rifampicin, rifabutin, rifapentine, st john warts, itraconazole, ketoconazole, midazolam, sertraline, sofosbuvir, atanzanair, darunavir, lopinavir

Tenofovir Disoproxil Fumarate (TDF)

ATC code: J05AF07

Tablet, 300 mg (tenofovir disoproxil fumarate equivalent to 245 mg tenofovir disoproxil), LOU 2

Indications and dose

Adult

HIV infection (in combination with other antiretroviral medicines): 245 mg (1 tablet) once daily

Contraindications: Hypersensitivity to active substance or any of the excipients

Precautions: renal impairment, hepatic disease, pregnancy, breastfeeding

Hepatic impairment: Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis have been reported. Exercise caution in patients (particularly obese women) with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa and ribavirin), liver enzyme abnormalities, or risk factors for liver disease and hepatic steatosis (including alcohol abuse) and discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly, or lactic acidosis occurs. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of tenofovir.

Adverse effects: nausea, vomiting, abdominal pain, flatulence, diarrhoea, anorexia, hypophosphataemia, dizziness, peripheral neuropathy, headache, dyspnoea, insomnia, depression, asthenia, sweating, myalgia, rash, hypertriglyceridaemia, hyperglycaemia, neutropenia, nephritis, nephrogenic diabetes insipidus, renal impairment, effects on renal proximal tubules (including Fanconi syndrome), proteinuria, polyuria, reduced bone density, pancreatitis, hepatitis, lactic acidosis, raised liver enzymes, creatinine, and serum amylase reported

Notes:

» Patient advice: Tablets can be dispersed in at least 100 mL water, orange juice, or grape juice for patients with difficulty swallowing.

Zidovudine (ZDV)

ATC code: J05AF01

Oral liquid, 10 mg/mL (50 mg/5 mL), LOU 2

Tablet, 300 mg, LOU 2

Adult

Indications and dose

HIV infection (in combination with other antiretroviral medicines): 500–600 mg daily in 2–3 divided doses

Paediatric

Prevention of mother-to-child transmission of HIV, oral

Neonate or **infant:** 4 mg/kg every 12 hours starting within 12 hours after birth and continuing up to 1–6 weeks of age, depending on national recommendations

HIV infection, in combination with other antiretroviral drugs, oral

Infant over 6 weeks old: 180–240 mg/m2 twice daily, maximum 300 mg twice daily

Zidovudine: Recommended dosing using 300-mg tablets according to weight bands.

Weight range (kg) 180–240 mg/m2 twice daily		Target dose	Dose (tablets)	
minimum (Kg)	maximum (Kg)	Formulation	a.m.	p.m.
25	29.9	300-mg tablet	1	1
30	34.9	300-mg tablet	1	1

Zidovudine: Recommended dosing using oral liquid and 300-mg tablets according to weight bands.

Weight range (kg) Infants > 6 weeks old: 180–240 mg/m2 twice daily Maximum dose 300 mg twice daily		Target dose	Dose (mL or tablets)	
minimum (Kg)	maximum (Kg)	Formulation	a.m.	p.m.
3	3.9	10-mg/mL syrup	6 mL	6 mL
4	4.9	10-mg/mL syrup	6 mL	6 mL
5	5.9	10-mg/mL syrup	6 mL	6 mL
6	6.9	10-mg/mL syrup	9 mL	9 mL

7	7.9	10-mg/mL syrup	9 mL	9 mL
8	8.9	10-mg/mL syrup	9 mL	9 mL
9	9.9	10-mg/mL syrup	9 mL	9 mL
10	10.9	10-mg/mL syrup	12 mL	12 mL
11	11.9	10-mg/mL syrup	12 mL	12 mL
12	13.9	10-mg/mL syrup	12 mL	12 mL
14	16.9	300-mg tablet	0.5	0.5
17	19.9	300-mg tablet	0.5	0.5
20	24.9	300-mg tablet	1	0.5
25	29.9	300-mg tablet	1	1
30	34.9	300-mg tablet	1	1

Contraindications: Abnormally low neutrophil counts or haemoglobin, neonates either with hyperbilirubinaemia requiring treatment other than phototherapy or with raised transaminase, acute porphyria.

Precautions: Haematological toxicity, including vitamin B12 deficiency, anaemia and myelosuppression, renal impairment, chronic hepatitis B or C.

Hepatic impairment: Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported. Exercise caution in patients with hepatomegaly, hepatitis, liver enzyme abnormalities, or risk factors for liver disease and hepatic steatosis, discontinue if there is any rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis.

Renal impairment: Severe: reduce dose.

Hepatic impairment: Dosage adjustment may be required, accumulation may occur. Use with caution, monitor for haematological toxicities frequently.

Adverse effects: Common: Haematological toxicity, including neutropenia, leukopenia and anaemia, severe headache, malaise, nausea, vomiting, anorexia. Rare: Myopathy (associated with prolonged use), myositis, liver toxicity, lactic acidosis, severe hepatomegaly with steatosis, fat redistribution (see Lipodystrophy, below), skin and nail pigmentation, neuropathy. Note: Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (*indicates serious):

Note: Increased risk of toxicity with nephrotoxic and myelosuppressive drugs.

Fluconazole: increased plasma concentration of zidovudine (increased risk of toxicity).

Ganciclovir: increased risk of haematological toxicity.

Interferon alfa: increased risk of hepatic and haematological toxicity.

Phenytoin: plasma phenytoin concentration increased or decreased by zidovudine.

Pyrimethamine: increased antifolate effect.

Ribavirin: increased risk of hepatic and haematological toxicity.

Rifampicin: avoidance of rifampicin advised by manufacturer of zidovudine.

Stavudine: may inhibit effect of stavudine (avoid concomitant use).

Valproic acid: plasma concentration of zidovudine possibly increased (risk of toxicity).

Notes:

- Do not use stavudine with zidovudine due to an antagonistic effect.
- Can be given without regard to food.
- Capsules can be opened and dissolved in water. Administer immediately.
- Tablets may be crushed and combined with a small amount of food and administered immediately.
- Store oral liquid at room temperature and protect from light.
- For intermittent IV infusion, dilute to concentration 2 mg/mL or 4 mg/mL with glucose 5% and give over 1 hour, or 30 minutes in neonates.
- Do not administer by IM injection, IV push or rapid infusion.
- Exercise extreme caution with abbreviations.

7.4.2.2. Non-nucleoside Reverse Transcriptase Inhibitors

Dapivirine Vaginal Ring

ATC code: G01AX17

Vaginal delivery system, 25 mg, LOU 2

Indications and dose

Adult

Pre-exposure prophylaxis of HIV-1 infection: One Dapivirine Vaginal Ring is inserted into the vagina and kept in until replaced each month with a new ring. To maintain efficacy, a new Dapivirine Vaginal Ring should be inserted immediately after the previous ring is removed.

Contraindications: Hypersensitivity to dapivirine, Use in women with unknown or positive HIV status.

Precautions: Only reduces the risk of HIV-1 infection in women by vaginal intercourse. should not be removed prior to, during or after vaginal sexual intercourse, use of vaginal clotrimazole.

Pregnancy: There is limited amount of data of use in pregnant women pregnant women. The benefits of treatment should be considered for pregnant women at high risk of HIV infection, considering the subsequent risk of HIV transmission to the unborn child.

Breastfeeding: No formal studies have been conducted in women who are breast-feeding

Adverse effects: Urinary tract infection, vaginal discharge, vulvovaginal pruritus, vulvovaginitis, pelvic pain, dysuria, lower abdominal pain.

Interactions with other medicines: Vaginal miconazole, contraceptives or diaphragms

Notes:

- Can be used with condoms and both should be used during vaginal sexual intercourse.
- Should remain in the vagina during menses and can be used with tampons.

» Contact with vaginal fluids, and blood during menses, may change the color of the ring during use. Such discoloration does not affect the mechanism of action.

Etravirine (ETV)

ATC code: J05AG04

Tablet, 25 mg, 100 mg, 200 mg, LOU 3

Indications and dose

Adult

HIV infection resistant to other non-nucleoside reverse transcriptase inhibitor and protease inhibitors in combination with other antiretroviral drugs (including a boosted protease inhibitor): 200 mg twice daily, to be taken after food.

Paediatric

Given orally with other antiretroviral drugs in managing HIV infection and AIDS in treatment-experienced children and adolescents aged 6 to 18 years; doses should be taken after food and are based on body weight.

16 to <20 kg: 100 mg twice daily

20 to <25 kg: 125 mg twice daily

25 to <30 kg: 50 mg twice daily

At least 30 kg: 200 mg twice daily (maximum dose)

Contraindications: Acute porphyrias

Hepatic impairment: Use with caution in moderate impairment and in patients with hepatitis B or C (increased risk of hepatic adverse effects), avoid in severe impairment (no information available).

Adverse effects: Common or very common: Diabetes mellitus, diarrhoea, headache, hyperglycaemia, MI, nausea, skin reactions, vomiting. Uncommon: Angioedema, bronchospasm, dry mouth, dyslipidaemia, gynaecomastia, haematemesis, hepatic disorders, hyperhidrosis, hypersensitivity, hypersomnia, numbness, pancreatitis, sluggishness, vision blurred. Rare or very rare: SCARs. Frequency not known: Haemorrhagic stroke, osteonecrosis, weight increased. Hypersensitivity reactions: Rash, usually in the second week, is the most common side-effect and appears more frequently in females. Life-threatening hypersensitivity reactions reported usually during week 3–6 of treatment and characterised by rash, eosinophilia, and systemic symptoms (including fever, general malaise, myalgia, arthralgia, blistering, oral lesions, conjunctivitis, and hepatitis). Discontinue permanently if hypersensitivity reaction or severe rash develop. If rash mild or moderate (without signs of hypersensitivity reaction), may continue without interruption—usually resolves within 2 weeks.

Notes:

» DIRECTIONS FOR ADMINISTRATION: Patients with swallowing difficulties may disperse tablets in a glass of water just before administration.

» Missed doses If a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Nevirapine (NVP)

ATC code: J05AG01

Oral liquid, 10 mg/mL, LOU 2

Indications and dose:

Progressive or advanced HIV infection, in combination with at least two other antiretroviral drugs, prevention of mother-to-child transmission.

Adult

HIV infection (in combination with other antiretroviral medicines), oral: 200 mg once daily for first 14 days, then (if no rash present) 200 mg twice daily,

Prevention of mother-to-child transmission of HIV, oral: 200 mg as a single dose at onset of labour

Note: In adults, if treatment is interrupted for more than 7 days, reintroduce at a dose of 200 mg daily and increase dose cautiously.

Paediatric:

Progressive or advanced HIV infection, in combination with other antiretroviral drugs, oral

Neonate, Infant or **Child:** initially 160–200 mg/m2 (maximum 200 mg) once daily for the first 14 days, increasing to twice daily after 14 days in the absence of nevirapine-induced rash (see Special considerations on dosing, below).

Special considerations on dosing:

Induction dose: once daily for first 14 days, it is generally half the daily maintenance dose given once daily except where the maintenance dose is divided unequally between a.m. and p.m.

Maintenance dose: target dose is 160–200 mg/m2 given twice daily and adjusted for more aggressive dosing in the younger age group.

If a mild rash occurs during the first 14 days of induction dosing, continue once daily dosing and only escalate dose once the rash has subsided and the dose is well tolerated. If a severe rash occurs (especially if accompanied by fever, blistering or mucosal ulcerations), discontinue drug.

Note: If treatment interrupted for more than 7 days, reintroduce with lowest dose and increase dose cautiously.

Simplified dosing tables based on weight bands are designed around 50 mg tablets

Nevirapine: Recommended maintenance dosing using 50-mg tablet according to weight bands.

Weight range (kg)	Target dose		Dose (tablets)	
	Maintenance dose after 2week induction: 160–200 mg/m2 to maximum 200 mg twice daily			
minimum (Kg)	maximum (Kg)	Formulation	a.m.	p.m.
3	3.9	50 mg tablet	1	1
4	4.9	50 mg tablet	1	1
5	5.9	50 mg tablet	1	1
6	6.9	50 mg tablet	2	1

7	7.9	50 mg tablet	2	1
8	8.9	50 mg tablet	2	1
9	9.9	50 mg tablet	2	1
10	10.9	50 mg tablet	2	2
11	11.9	50 mg tablet	2	2
12	13.9	50 mg tablet	2	2
14	16.9	50 mg tablet	3	2
17	19.9	50 mg tablet	3	2
20	24.9	50 mg tablet	3	3

Prevention of mother-to-child transmission of HIV, oral

Neonate: 2 mg/kg as a single dose within 72 hours of birth, if the maternal dose is given less than 2 hours before delivery, 2 mg/kg should be given immediately after birth, followed by a further dose within 24–72 hours.

Note: If treatment is interrupted for more than 7 days, reintroduce at a dose of

Infant 15–30 days old: 5 mg/kg,

Child over 1 month: 120 mg/m2)

and increase dose cautiously.

Contraindications: Moderate or severe hepatic impairment, post-exposure prophylaxis.

Precautions: Hepatic impairment (see below), rash (see below), chronic hepatitis B or C, high CD4 cell count (preferably avoid in women with CD4 cell count greater then 250cells/mm3 or in men with CD4 cell count greater than 400 cells/mm3).

Adverse effects: Hepatic disease: Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually in the first 6 weeks, close monitoring required during first 18 weeks, assess liver function before treatment then every 2 weeks for 2 months, then after 1 month and then regularly, discontinue permanently if liver abnormalities accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia), suspend if severe liver abnormalities but no hypersensitivity reaction, discontinue permanently if significant liver function abnormalities recur, monitor patient closely if mild to moderate liver abnormalities with no hypersensitivity reaction.

Rash, usually in first 6 weeks, is most common side-effect, incidence reduced if introduced at low dose and dose increased gradually, monitor closely for skin reactions during first 18 weeks, discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, facial oedema, general malaise or hypersensitivity reactions, if rash mild or moderate, may continue without interruption but dose should not be increased until rash resolves.

Notes:

» Patient advice: Patients and/or caregivers should be educated on how to recognize hypersensitivity reactions and advised to discontinue treatment and seek immediate medical attention if symptoms of hepatitis, severe skin reaction or hypersensitivity reactions develop.

7.4.2.3. Protease Inhibitors (PI)

Atazanavir + Ritonavir (ATV+R)

ATC code: J05AR23

Tablet (heat-stable), 300 mg + 100 mg, LOU 2

Indications and dose

Adult

Recommended in treatment of HIV. When atazanavir and ritonavir are taken together, ritonavir will "boost" the level of atazanavir and increase its effect.

The usual adult dose is atazanavir 300 mg (1 × 300 mg capsule OR 2 × 150 mg capsules) once daily, with ritonavir 100 mg (1 tablet or capsule) once daily.

Paediatric

Oral, target dose

Child over 6 years 15 kg up to 25 kg: 150 mg atazanavir and 80 mg ritonavir once daily

Child 25–30 kg: 200 mg atazanavir and 100 mg ritonavir once daily

Child 30 kg and over: 300 mg atazanavir and 100 mg ritonavir once daily (maximum dose)

Recommended for patients from 6 years of age; currently insufficient data for patients under 6 years of age

For contraindications and precautions: see individual drug monographs

Adverse effects: Common: nausea, diarrhea, vomiting, anorexia, abdominal pain, taste disturbances and abnormal sensations in the hands, feet or in and around the mouth.

Other effects may include: headache, muscle weakness, fever, lightheadedness, insomnia and/or sweating.

Notes:

» Atazanavir and ritonavir should be taken at the same time.

» The medication should be taken with food (i.e. a light meal) to increase absorption.

» The capsules or tablets should be swallowed whole (do NOT chew).

» Atazanavir absorption can be significantly lowered by medications that decrease stomach acidity (e.g., ranitidine, cimetidine, famotidine, omeprazole, pantoprazole) These medicines must be taken at least 1 hour before or 2 hrs after the dose of atazanavir.

» Alcohol is not recommended in the first 4 weeks of therapy and should be used with caution thereafter.

Darunavir (DRV)

ATC code: J05AE10

Tablet, 75 mg, 150 mg, LOU 3

Tablet (f/c), 600 mg, LOU 3

Oral liquid, 10 mg/mL (200 mL), LOU 3

Indications and dose

Adult

ART-naive patients, oral: the recommended dose of darunavir is 800 mg (with ritonavir 100 mg) once daily with food.

ART-experienced patients, oral: doses are generally chosen based on the degree of darunavir resistance seen via genotypic testing; however, where testing is not feasible, a dose of 600 mg (with ritonavir 100 mg) twice daily is recommended.

Paediatric

It is recommended that darunavir be reserved for ART treatment-experienced children only. The following oral doses are recommended, based on body weight:

20 to <30 kg: Darunavir 375 mg (with ritonavir 50 mg) twice daily

30 to <40 kg: Darunavir 450 mg (with ritonavir 60 mg) twice daily

40 kg and over: Darunavir 600 mg (with ritonavir 1 00 mg) twice daily

Contraindication: Hypersensitivity to the active substance or to any of the excipients. Patients with severe (Child-Pugh Class C) hepatic impairment.

Precautions: Patients should undergo liver function tests before starting and during treatment with darunavir. It should not be used in patients with severe hepatic impairment (Child-Pugh class C) and should be used with caution (and liver enzymes values monitored), in those with mild to moderate impairment (Child-Pugh A or B) and those with chronic hepatitis B or C co-infection. Patients co-infected with chronic hepatitis B or C and treated with combination ART are at increased risk for severe and potentially fatal hepatic adverse events. All patients should be instructed to seek medical advice if symptoms suggestive of new or worsening hepatotoxicity occur. Darunavir contains a sulfonamide moiety and should be used with caution in patients with known sulfonamide hypersensitivity, although its cross-sensitivity potential with sulfonamide drugs is unknown. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 365.3.) Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HN-protease inhibitors. An association with erythema multiforme and SJS has been reported and treatment should be stopped in patients who develop severe rashes.

Hepatic impairment: The safety and efficacy of darunavir have not been established in patients with severe underlying liver disorders and darunavir is therefore contraindicated in patients with severe hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, darunavir should be used with caution in patients with mild or moderate hepatic impairment

Pregnancy: Should be used during pregnancy only if the potential benefit justifies the potential risk.

Adverse Effects:

- The most common adverse effects associated with antiretroviral regimens containing darunavir are GI disturbances (abdominal pain, diarrhoea, nausea, and vomiting), nasopharyngitis, and hypertriglyceridaemia. Rashes (usually of mild to moderate severity) are seen in about 5 to 10% of patients, typically occurring within the first 4 weeks of treatment and resolving without stopping treatment. Severe rashes, including erythema multiforme and SJS, have occurred more rarely, treatment should be stopped if severe rash develops.
- Other reported adverse effects are asthenia, dizziness, fatigue, headache, and insomnia. Less frequently reported adverse effects include folliculitis, MI, osteopenia, osteoporosis, polyuria, somnolence, tachycardia, transient ischaemic attacks, and vertigo. Cases of drug-induced hepatitis, including fatalities, have been reported. Abnormal liver and pancreatic function tests, anaemia, neutropenia, and thrombocytopenia have also occurred.
- Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination ART, including darunavir, in HIV-infected patients with severe immune deficiency.
- Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving ART, including damnavir.
- Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV -protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination ART.

Darunavir + Ritonavir (DRV+R)

ATC code: JO5AR26

Tablet , 600mg + 100mg, 800mg + 100mg, LOU 3

Indications and dose

Adult

HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretroviral

therapy: 600 mg twice daily (taken with food), alternatively 800 mg once daily (once daily dose only to be used if no resistance to darunavir, if plasma HIV-RNA concentration less than 100 000 copies/mL, and if CD4 cell count greater than 100 cells×106 / liter)

Paediatric

HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretroviral therapy (third line regimen)

Child 3–17 years: (15-29kg) 375mg twice daily

Child 3–17 years: (30-39kg) 450mg twice daily

Child 3–17 years: (40kgs and above) 600mg twice daily

Child 12–17 years: 800mg once daily (once daily dose only to be used if no resistance to darunavir, if plasma HIV-RNA concentration less than 100 000 copies/mL, and if CD4 cell count greater than 100 cells×106 / liter)

Contraindications: Hypersensitivity to darunavir, patients with severe hepatic impairment, combination with strong CYP3A inducers such as rifampicin. Contraindicated in patients with hemophilia type A and B

Precautions: Pediatric populations below 3 years or below 15kgs not recommended. Use cautiously in elderly patients 65 years and over due to reduced liver function.

Hepatic impairment: Use with caution in mild to moderate liver impairment, Contraindicated in patients with severe liver impairment

Renal impairment: Refer to the individual medicines

Pregnancy: use only if potential benefit outweighs risk

Breastfeeding: Potential adverse reactions in breast fed infants, women should not breastfeed when using darunavir

Adverse effects: Osteonecrosis, diarrhea, nausea, vomiting, rash, headache, acute renal failure, myocardial infarction, Immune reconstitution inflammatory Syndrome (IRIS), thrombocytopenia, hepatitis, pyrexia, neutropenia, anemia, hypothyroidism, gout, decreased apetite, hypoglycemia, insomnia, depression, anxiety, decreased libido, peripheral neuropathy, dyspepsia, abdominal distention, increased pallor, increased ALT, asthenia, fatigue.

Interactions with other medicines (*indicates serious): St john wort, alfuzosin, amiodarone, quinidine, astemizole, tafenadine, ergot derivatives, cisapride, dapoxetine, domperidone, sildenafil, simvastatin, ticagrelor, triazolam, midazolam, pimozide, Efavirenz, *colchicine, quetiapine

Lopinavir + Ritonavir (LPV+R)

ATC code: J05AR10

Tablet (heat stable), 100 mg + 25 mg, 200 mg + 50 mg, LOU 2

Granuels (in sachet), 40 mg + 10 mg, LOU 2

Indications and dose

HIV infection, in combination with other antiretroviral drugs

Note: Ritonavir increases the effect of lopinavir; the low doses of ritonavir used for this purpose do not have intrinsic antiviral activity.

Adult

HIV infection (in combination with other antiretroviral medicines), oral: 3 capsules or 5 mL twice daily (lopinavir, 400 mg + ritonavir, 100 mg twice daily)

Paediatric

HIV infection (in combination with other antiretroviral medicines), oral

Child 6 month–13 years: Lopinavir 225 mg/m2 + ritonavir 56.25 mg/m2 twice daily OR

Child body weight 7–15 kg: Lopinavir 12 mg/kg + ritonavir 3 mg/kg twice daily

Child body weight 15–40 kg: Lopinavir 10/mg/kg + ritonavir 2.5 mg/kg twice daily

Adolescent with BSA of 1.3 m2 or greater: 3 capsules or 5 mL twice daily (lopinavir, 400 mg + ritonavir, 100 mg twice daily)

Lopinavir + Ritonavir: Recommended dosing using tablets according to weight bands

Weight range (kg)		Lopinavir target doses	Dose (mL)	
		5–7.9 kg: 16 mg/kg twice daily **8–9.9 kg:** 14 mg/kg twice daily **10–13.9 kg:** 12 mg/kg twice daily **14–39.9 kg:** 10 mg/kg twice daily		
		Ritonavir target doses		
		7–15 kg: 3 mg/kg twice daily **15–40 kg:** 2.5 mg/kg twice daily		
		Maximum dose		
		400 mg lopinavir + 100 mg ritonavir twice daily		
Minimum (kg)	**Maximum (kg)**	**Formulation (per mL solution)**	**a.m.**	**p.m.**
10	10.9	100 mg lopinavir+25 mg ritonavir	2	1
11	11.9	100 mg lopinavir+25 mg ritonavir	2	1
12	13.9	100 mg lopinavir+25 mg ritonavir	2	1
14	16.9	100 mg lopinavir+25 mg ritonavir	2	2
17	19.9	100 mg lopinavir+25 mg ritonavir	2	2
20	24.9	100 mg lopinavir+25 mg ritonavir	3	2
25	29.9	100 mg lopinavir+25 mg ritonavir	3	3
30	34.9	100 mg lopinavir+25 mg ritonavir	3	3

Lopinavir + ritonavir: Recommended dosing using Granules according to weight bands

Weight range (kg)			Dose (Number of sachets)	
Bottom	**Top**	**Formulation (per sachet)**	**a.m.**	**p.m.**
3	5.9	40 mg lopinavir + 10 mg ritonavir	2	2
6	9.9	40 mg lopinavir + 10 mg ritonavir	3	3
10	13.9	40 mg lopinavir + 10 mg ritonavir	4	4
14	19.9	40 mg lopinavir + 10 mg ritonavir	5	5
20	24.9	40 mg lopinavir + 10 mg ritonavir	6	6

Contraindications: Severe hepatic impairment, severe renal impairment, porphyria.

Precautions: Chronic hepatitis B or C (increased risk of hepatotoxicity), hepatic impairment, renal impairment, haemophilia, pancreatitis (see below), diabetes mellitus, cardiac conduction disorders, structural heart disease, concomitant use with drugs that prolong QT interval, oral solution contains propylene glycol: increased susceptibility to propylene glycol toxicity in slow metabolizers. Pancreatitis: Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated, discontinue if pancreatitis diagnosed.

Renal impairment: Use with caution. Avoid oral solution (contains propylene glycol) in severe impairment. Use tablets with caution in severe impairment.

Hepatic impairment: Mild to moderate: avoid use of oral solution due to propylene glycol content. Use tablets and capsules with caution. Severe: avoid use.

Adverse effects: Common: Diarrhoea, headache, nausea, vomiting, rash, lipid abnormalities, asthenia, hypertension, insomnia, depression, amenorrhoea, raised hepatic enzymes. Tablets have less GI adverse effects than capsules. Uncommon: Pancreatitis, fat redistribution (lipoatrophy of peripheral fat and accumulation of central fat). Rare: Hepatitis, SJS, hyperglycaemia, new onset diabetes mellitus, exacerbation of existing diabetes mellitus, haemolytic anaemia, spontaneous bleeding in haemophiliacs, prolonged PR interval. Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Notes: Increase dose by 33% if used in combination with efavirenz or with nevirapine.

Patient advice: Each dose to be taken with food.

Ritonavir (RTV)

ATC code: J05AE03

Tablet (heat-stable), 100 mg, LOU 2

Oral powder, 100 mg sachet[C], LOU 2

Indications and dose

HIV infection, as a booster to increase the effect of indinavir, lopinavir, or saquinavir, in combination with at least two other antiretroviral medicines.

Adult

HIV infection (as a booster with other antiretroviral medicines), oral: 100 mg twice daily

Paediatric

HIV infection, as a pharmacological booster to increase other protease inhibitors, in combination with other antiretroviral drugs, oral

Child 7–14.9 kg: 3 mg/kg twice daily

Child 15–40 kg: 2.5 mg/kg twice daily (maximum 100 mg twice daily)

Precautions: Cardiac conduction disorders, pancreatitis, structural heart disease

Renal impairment: No dosage adjustment necessary (renal clearance is negligible).

Hepatic impairment: Mild to moderate: no dosage adjustment recommended. Severe: avoid in severe hepatic impairment, if no alternative, use with extreme caution.

Adverse effects: nausea, vomiting, diarrhoea (may impair absorption -close monitoring required), abdominal pain, taste disturbances, dyspepsia, anorexia, throat irritation, vasodilatation, hypotension, syncope, headache, drowsiness, circumoral and peripheral paraesthesia, hyperaesthesia, dizziness, sleep disturbances, fatigue, rash, hypersensitivity reactions, leukopenia, seizures, raised liver enzymes, bilirubin, and uric acid, occasionally flatulence, eructation, dry mouth and ulceration, cough, anxiety, fever, pain, menorrhagia, myalgia, myositis, rhabdomyolysis, weight loss, decreased thyroxine, sweating, pruritus, electrolyte disturbances, anaemia, neutropenia, and increased PT, pancreatitis (see also note on Pancreatitis, above), lipodystrophy and metabolic effects (see also introductory note above). Uncommon: Vasodilatation, hypotension, syncope, dizziness, dehydration, renal insufficiency, fat redistribution (see Lipodystrophy, below), exacerbation of liver disease. Rare: Hyperglycaemia, new onset diabetes mellitus, exacerbation of existing diabetes mellitus, spontaneous bleeding in haemophiliacs, pancreatitis, hepatitis, menorrhagia, seizures, prolongation of PR interval, atrioventricular block. Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines: Co-administration of ritonavir and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects.

Notes:

- Unpleasant/foul taste may require special techniques to increase tolerance in children.
- Oral solution can be mixed with milk, chocolate pudding or ice cream. Do not mix with other liquids or water. Oral solution should be stored at room temperature. Do not refrigerate. Shake well before use.
- Administer strong flavoured foods, such as maple syrup, cheese or jam, immediately after dose.
- Store soft gelatin capsules in fridge until dispensed. Patient can store in fridge or store at room temperature (use within 30 days).
- Give with food to increase absorption and reduce GI adverse effects.
- If prescribed with didanosine, separate drugs by 2 hours.
- Capsules and liquid formulations contain alcohol as a major excipient.

7.4.2.4. Integrase Inhibitors

Cabotegravir

ATC code: JOFAJO4

Injection, 600mg/3mL (Prolonged release suspension), LOU 2

Indications and dose

Adult

Pre-exposure prophylaxis for HIV: Initiation injections: 600 mg Intramuscular (IM) x 2 doses given 1 month apart (the second initiation injection can be given up to 7 days before or after the date scheduled to receive injection) then Continuation injections: 600 mg IM every 2months.

Contraindications: Hypersensitivity to cabotegravir

Precautions: Co-infection with hepatitis B or C risks virologic failure

Hepatic impairment: Use with caution in severe hepatic impairment

Renal impairment: Increased monitoring in severe renal impairment

Pregnancy: Avoid unless potential benefits outweighs the risk

Breastfeeding: Avoid, present in milk in animal studies

Adverse effects (*indicates serious): Rash, liver injury, hepatoxicity, IRIS, hypercreativity, depression, anxiety, insomnia, abnormal dreams, headache, dizziness, somnolence, suicidal ideation, nausea, vomiting, diarrhea, abdominal pain, flatulence, hepatoxicity, rash, *urticaria, *angioedema, myalgia, fatigue, pyrexia, asthenia, malaise, injection site reactions(uncommon), weight gain, increase transaminases and bilirubin.

Interactions with other medicines: Rifampicin, rifapentine, carbamazepine, oxcarbamazepine, phenytoin, phenobarbitone

Dolutegravir (DTG)

ATC code: J05AJ03

Tablet, 10mg, 50 mg, LOU 2

Tablet (despersible), 10 mg, LOU 2

Indications and dose

HIV infection without resistance to other inhibitors of HIV integrase, in combination with other antiretroviral drugs

Adult

Indicated in combination with other ARTs in adults; Integrase strand transfer inhibitor (INSTI) indicated in patients who weigh 30 kg or greater; Treatment-naïve or treatment-experienced INSTI-naïve, oral: 50 mg once daily

INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance: 50 mg twice daily

Paediatric

HIV infection without resistance to other inhibitors of HIV integrase, in combination with other antiretroviral drugs, oral

Child >4weeks (3-5.9kg): 5mg once daily

Child >4weeks (6-9.9kg): 15mg once daily

Child >4weeks (10-13.9kg): 20mg once daily

Child >4weeks (14-19.9kg): 25mg once daily

Child >4weeks (>20kg): 50mg once daily

Child 12–17 years (body weight 40 kg and above): 50 mg once daily

HIV infection in combination with other antiretroviral drugs (with concomitant carbamazepine, efavirenz, etravirine [without boosted protease inhibitors, but see also interactions], fosphenytoin, phenobarbital, phenytoin, primidone, nevirapine, oxcarbazepine, St John's wort, rifampicin, or tipranavir), oral

Child 12–17 years (body weight 40 kg and above): 50 mg twice daily

Note: Avoid concomitant use with these drugs if resistance to other inhibitors of HIV integrase is suspected.

Hepatic impairment: Manufacturer advises caution in severe impairment—no information available

Pregnancy Manufacturer advises avoid, see Important Safety Information.

Adverse effects: Common or very common: Depression, diarrhea, dizziness, fatigue, flatulence, GI discomfort, headache, nausea, skin reactions, sleep disorders, vomiting. Uncommon: Arthralgia, hepatitis, hypersensitivity, immune reconstitution inflammatory syndrome, myalgia, suicidal tendencies. Hypersensitivity reactions (including severe rash, or rash accompanied by fever, malaise, arthralgia, myalgia, blistering, oral lesions, conjunctivitis, angioedema, eosinophilia, or raised liver enzymes) reported uncommonly. Discontinue immediately if any sign or symptoms of hypersensitivity reactions develop. Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination ART.

7.4.2.5. Fixed-Dose Combinations

Abacavir + Lamivudine (ABC+3TC)

ATC code: J05AR02

Tablet (dispersible, scored), 120 mg (as sulphate) + 60 mg, LOU 2

Tablet, 600 mg (as sulphate) + 300 mg, LOU 2

Indications and dose

Adult

HIV infection in combination with other antiretroviral drugs, oral: 1 tablet (600 mg abacavir/300 mg lamivudine) once daily

Paediatric

Adolescents and children weighing at least 25 kg: One tablet abacavir/lamivudine (600 mg abacavir/300 mg lamivudine) once daily

Child under 25 kg: Should not be administered to children weighing <25 kg because it is a fixed-dose tablet that cannot be dose reduced.

The safety and efficacy of abacavir/lamivudine in children weighing <25 kg has not been established.

Contraindications: Hypersensitivity to the active substances or to any of the excipients

Precautions:

Elderly: No pharmacokinetic data are currently available in patients over 65 years of age. Special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

Renal impairment: Abacavir/Lamivudine is not recommended for use in patients with a CrCl < 50 mL/min as necessary dose adjustment cannot be made

Hepatic impairment: Abacavir is primarily metabolised by the liver. No clinical data are available in patients with moderate or severe hepatic impairment, therefore the use of abacavir/lamivudine is not recommended unless judged necessary. In patients with mild hepatic impairment (Child-Pugh score 5-6) close monitoring is required, including, monitoring of abacavir plasma levels if feasible

Hypersensitivity reactions: Abacavir is associated with a risk for hypersensitivity reactions characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSRs have been observed with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately.

Notes:

» Abacavir/lamivudine is a fixed-dose tablet and should not be prescribed for patients requiring dose adjustments. Separate preparations of abacavir or lamivudine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated.

In these cases the physician should refer to the individual product information for these medicinal products.

» While effective viral suppression with ART has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Tenofovir Alafenamide + Lamivudine + Dolutegravir (TAF+3TC+DTG)

ATC code: NA

Tablet, 25 mg +300 mg +50 mg, LOU 2

Indications and dose

Adult

Treatment of HIV-1 infection: One tablet daily

Paediatric

Treatment of HIV-1 infection:

Child >40kg: One tablet daily

Contraindications: Hypersensitivity reaction to dolutegravir, lamivudine, or tenofovir alafenamide.

Precautions: See individual monographs

Hepatic impairment: See individual monographs

Renal impairment: See individual monographs

Pregnancy: See individual monographs

Breastfeeding: See individual monographs

Adverse effects: See individual monographs

Interactions with other medicines (*indicates serious): See individual monographs

Notes: See individual monographs

Tenofovir Disoproxil Fumarate + Emtricitabine (TDF+FTC)

ATC code: J05AR03

Tablet, 300 mg + 200 mg, LOU 2

Indications and dose

Adult and adolescent weighing at least 35 kg

HIV infection in combination with other antiretroviral (ART) agents, oral: One 300 mg/200 mg tablet once daily

HIV-1 pre-exposure prophylaxis indicated in combination with safer sex practices to reduce risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing ≥35 kg: One 300 mg/200 mg tablet once daily

PrEP indications:

» Men who have sex with men at substantial risk of HIV acquisition

» Adult heterosexually active men and women at substantial risk of HIV acquisition

» Adult injection-drug users at substantial risk of HIV acquisition

» Heterosexually active women and men whose partners are known to have HIV infection (i.e., HIV-discordant couples) to protect the uninfected partner during conception and pregnancy so that an informed decision can be made in awareness of what is known and unknown about benefits and risks of PrEP for mother and fetus

Contraindications: Do not use for pre-exposure prophylaxis in individuals with unknown or positive HIV-1 status. should be used in HIV-infected patients only in combination with other antiretroviral agents.

Hepatic impairment: No substantial alterations in tenofovir pharmacokinetics observed in clinical trials in subjects with hepatic impairment compared with unimpaired subjects

Pharmacokinetics of emtricitabine have not been studied with hepatic impairment, however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited

Adverse Effects: Lactic Acidosis/Severe Hepatomegaly with Steatosis, Severe Acute Exacerbations of hepatitis B, New Onset or Worsening Renal Impairment, Bone Effects of Tenofovir DF, Immune Reconstitution Syndrome.

Notes:

» **HIV infection:**

Should not be coadministered with combination products that are complete regimens or already contain emtricitabine and/or tenofovir or a regimen containing a nucleotide reverse transcriptase inhibitor

because of similarities in mechanism of action between these agents.

» **PrEP:**

Individuals must have a negative HIV-1 test immediately prior to initiating emtricitabine/tenofovir AF for HIV-1

If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test cleared by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection

Continuing screening at least once every 3months while taking emtricitabine/tenofovir AF

» **Dosing Considerations:**

All patients should be tested for the presence of chronic HBV before or when initiating

Before initiating and during use, on a clinically appropriate schedule, assess serum creatinine, estimated CrCl, urine glucose and urine protein in all patients, in patients with chronic kidney disease (CKD), also assess serum phosphorus

Tenofovir Disoproxil Fumarate + Lamivudine (TDF+3TC)

ATC code: J05AR12

Tablet, 300 mg + 300 mg, LOU 2

Indications and dose

Adult and adolescent weighing >35 kg

HIV infection in combination with other antiretroviral

agents, oral: 1 tablet (lamivudine 300 mg/ tenofovir 300 mg)

Paediatric: Lamivudine/tenofovir disoproxil tablet is not recommended for use in children and adolescents below the age of 18 years because of insufficient data on safety and efficacy.

Contraindications: Previous hypersensitivity reaction to either active component or to any of the ingredients. Safety and efficacy have not been established in patients weighing less than 35 kg.

Precautions:

Post-treatment acute exacerbations of hepatitis B: Severe acute exacerbations of hepatitis B reported in patients coinfected with HBV and HIV-1 who have stopped lamivudine or tenofovir disoproxil fumarate, components of this drug. Hepatic function of HBV/ HIV-1-coinfected patients should be monitored closely with clinical and laboratory follow-up for at least several months, if appropriate, antihepatitis B therapy should be started.

Renal impairment:

- CrCl ≥50 mL/min: No dosage adjustment necessary
- CrCl<50 mL/min or ESRD requiring hemodialysis: Not recommended because drug is a FDC tablet and dose cannot be adjusted

Hepatic impairment: Mild: No dosage adjustment necessary. Moderate-to-severe: Not recommended

Tenofovir Disoproxil Fumarate + Lamivudine + Dolutegravir (TDF+3TC+DTG), TLD

ATC code: J05AR27

Tablet, Tenofovir 300 mg + lamivudine 300 mg + dolutegravir 50 mg, LOU 2

Indications and dose

Adult

HIV/AIDs (is an FDC antiretroviral medication), oral: 1 tablet once daily in the morning

Paediatric

Child ≥30 kg and ≥10 years: 1 tablet once daily in the morning

Special considerations:

Use of TLD by women of child-bearing age	In July 2019, WHO announced that dolutegravir is safe for women of child-bearing age. Therefore, TLD is now the preferred first-line and second-line regimen for all populations, including pregnant women and those of child-bearing age.
	Exposure to dolutegravir around the time of conception and during the first 8 weeks of pregnancy was previously thought to be associated with an increased risk of neural tube defects in the fetus. The risks of neural tube defects are significantly lower than what the initial studies may have suggested.
Patients with HIV/TB coinfection	One of the anti-TB medications, rifampicin, lowers the level of dolutegravir when both are taken together.
	Therefore, patients who have diagnosed TB will need to modify their dolutegravir dose while they are taking rifampicin-containing anti-TB treatment.
	Patients with HIV/TB may take their usual dose of TLD (one tablet, once daily), but they need to add an additional dose of dolutegravir 50 mg 12 hours after taking their TLD.
	It is important to tell patients that the additional dose of dolutegravir must be taken 12 hours after their TLD, not at the same time (for example, take the TLD tablet in the morning and the dolutegravir single tablet in the evening).
Warnings and precautions	Previous hypersensitivity reaction to dolutegravir
	Uncontrolled diabetes
	Renal impairment CrCl <50 mL/min
	Liver impairment: ascites, albumin <2.8 g/dL, total bilirubin >50 mmol/L, encephalopathy

Adverse effects: Insomnia, Headache, Agitation, Nausea, Diarrhea, Skin rash (patients should contact their health care provider immediately if they develop a rash)

Tenofovir Disoproxil Fumarate + Lamivudine + Efavirenz (TDF+3TC+EFV)

ATC code: J05AR11

Tablet, Tenofovir 300 mg + lamivudine 300 mg +efavirenz 400 mg, LOU 2

Indications and dose

Adult

Complete antiretroviral (ART) regimen for HIV-1 infection, oral: 1 tablet once a day at bedtime

Paediatric

Child weighting 35 to 40 kg: 1 tablet once a day at bedtime

NB: Safety and efficacy have not been established in patients weighing less than 35 kg

Contraindications: Previous hypersensitivity reaction (e.g., SJS, erythema multiforme, or toxic skin eruptions) to any active component or any of the ingredients

Coadministration with elbasvir-grazoprevir

Renal impairment:

- CrCl ≥50 mL/min: No dosage adjustment necessary
- CrCl<50 mL/min or ESRD requiring hemodialysis: Not recommended because drug is a FDC tablet and dose cannot be adjusted

Hepatic impairment: Mild (Child-Pugh A): No dosage adjustment necessary. Moderate-to-severe (Child-Pugh

B or C): Not recommended

Adverse Effects: Most common adverse reactions are impaired concentration, abnormal dreams, headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, rash, dizziness, insomnia, pain, depression, asthenia, and cough.

Zidovudine + Lamivudine (AZT+3TC)

ATC code: J05AR01

Tablet, 300 mg + 150 mg, LOU 2

Indications and dose

Combination of 2 nucleoside analogues; indicated in combination with other antiretrovirals for treating HIV-1 infection

Adult

HIV-1, oral: 1 tablet (containing 150 mg of lamivudine and 300 mg of zidovudine) taken orally twice daily

Paediatric

Child ≥30 kg and for whom a solid oral dosage form is appropriate: 1 tablet administered orally twice daily

Before prescribing tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a tablet, liquid oral formulations (lamivudine oral solution and zidovudine syrup) should be prescribed.

Not Recommended Due to Lack of Dosage Adjustment

Because it is a fixed-dose tablet and cannot be dose adjusted, is not recommended for:

- Paediatric patients weighing less than 30 kg.
- Patients with CrCl less than 50 mL per minute.
- Patients with hepatic impairment.
- Patients experiencing dose-limiting adverse reactions.

Liquid and solid oral formulations of the individual components of COMBIVIR are available for these populations.

Adverse effects: Hematologic toxicity, including neutropenia and anemia, Symptomatic myopathy, Lactic acidosis and severe hepatomegaly with steatosis, Exacerbations of hepatitis B, Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C, Exacerbation of anemia in HIV-1/hepatitis C virus (HCV) co-infected patients receiving ribavirin and zidovudine, Pancreatitis, Immune reconstitution syndrome, Lipoatrophy.

7.4.2.6. Medicines for prevention of HIV-related opportunistic infections

Dapsone

ATC code: J04BA02

Tablet, 25 mg, 100 mg, LOU 2

Indications and dose

Adult

Mild to moderate Pneumocystis jirovecii, (Pneumocystis carinii) pneumonia (in combination with trimethoprim), oral: 100 mg once daily

Prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) pneumonia, oral: 100 mg daily

Paediatric

Mild to moderate Pneumocystis jirovecci, (Pneumocystis carinii) pneumonia (in combination with trimethoprim, oral

Child 1 month–11 years: 2 mg/kg once daily (max. per dose 100 mg)

Child 12–17 years: 100 mg once daily

Prophylaxis of Pneumocystis jirovecii, (Pneumocystis carinii) pneumonia

Child: 2 mg/kg once daily (max. per dose 100 mg)

Precautions: Anaemia (treat severe anaemia before therapy, and monitor blood counts during treatment), susceptibility to haemolysis including G6PD deficiency (including breastfeeding affected infants), porphyria. Blood disorders: On long-term treatment, patients and their Caregivers should be told how to recognize blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop.

Skilled tasks: Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Adverse effects: Common: GI irritation, photosensitivity. Rare: Haemolysis, methaemoglobinaemia, allergic dermatitis (rarely including toxic epidermal necrolysis and SJS), hepatitis, agranulocytosis, "dapsone syndrome" resembling mononucleosis (rare hypersensitivity reaction with symptoms including rash, fever, jaundice and eosinophilia), tachycardia, headache, nervousness, insomnia, blurred vision, paraesthesia, reversible peripheral neuropathy, psychoses.

Sulfamethoxazole + Trimethoprim (Co-Trimoxazole)

ATC code: J01EE01

Oral liquid ,240 mg/5 mL [c], LOU 2

Tablet, 800 + 160 mg, LOU 2

Indications and dose

Adult

Living with HIV: 960 mg daily (800 mg sulfamethoxazole + 160 mg trimethoprim)

Paediatric

Oral

Child 6 weeks–5 months: 120 mg twice daily, alternatively 24 mg/kg twice daily

Child 6 months–5 years: 240 mg twice daily, alternatively 24 mg/kg twice daily

Child 6–11 years: 480 mg twice daily, alternatively 24 mg/kg twice daily

Child 12–17 years: 960 mg twice daily

Contraindications: Acute porphyrias

Precautions: Asthma, avoid in blood disorders (unless under specialist supervision), avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia) because of the risk of kernicterus, G6PD deficiency (risk of haemolyticanaemia), maintain adequate fluid intake, predisposition to folate deficiency

Renal impairment: Avoid if EGFR less than 15 mL/min/1.73 m2 and if plasma-sulfamethoxazole concentration cannot be monitored. Dose adjustments Use half normal dose if EGFR 15–30 mL/min/1.73 m2. Monitoring Plasma concentration monitoring may be required in patients with moderate to severe renal impairment, seek expert advice.

Hepatic impairment: Manufacturer advises avoid in severe liver disease.

Pregnancy: Teratogenic risk in first trimester (trimethoprim a folate antagonist). Neonatal haemolysis and methaemoglobinaemia in third trimester, fear of increased risk of kernicterus in neonates appears to be unfounded.

Breastfeeding: Small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfamethoxazole).

Adverse effects: Common or very common: Diarrhoea, electrolyte imbalance, fungal overgrowth, headache, nausea, skin reactions. Uncommon: Vomiting. Rare or very rare: Agranulocytosis, angioedema, aplastic anaemia, decreased appetite, arthralgia, ataxia, cough, depression, dizziness, dyspnea, eosinophilia, fever, haemolysis, haemolytic anaemia, hallucination, hepatic disorders, hypoglycaemia, leucopenia, lung infiltration, megaloblastic anaemia, meningitis aseptic, metabolic acidosis methaemoglobinaemia, myalgia, allergic myocarditis, tubulointerstitial nephritis, neutropenia, oral disorders, pancreatitis, peripheral neuritis, photosensitivity reaction, pseudomembranous enterocolitis, renal impairment, renal tubular acidosis, seizure, serum sickness, SCARs, SLE, thrombocytopenia, tinnitus, uveitis, vasculitis, vertigo. Note: Co-trimoxazole is associated with rare but serious adverse effects. Discontinue immediately if blood disorders (including leucopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia) or rash (including SJS, toxic epidermal necrolysis) develop.

7.4.3. Other Antivirals

Ganciclovir

ATC code: J05AB06

Powder for injection, 500-mg vial, LOU 5

Indications and dose

Adult

CMV retinitis in immunocompromised adults, including patients with AIDS, induction: 5 mg/kg IV q12hr, infused over 1 hour for 14–21 days

Paediatric

Child: Initially 5 mg/kg every 12 hours for 14–21 days, then maintenance 6 mg/kg once daily, on 5 days of the week; alternatively, maintenance 5 mg/kg once daily; maintenance only for patients at risk of relapse; if disease progresses initial induction treatment may be repeated

Contraindications: Abnormally low haemoglobin count, abnormally low neutrophil count, abnormally low platelet count

Renal impairment: Induction dose adjustment:

- CrCl 50–69 mL/min: 2.5 mg/kg IV every 12hrs
- CrCl 25–49 mL/min: 2.5 mg/kg IV daily
- CrCl 10–24 mL/min: 1.25 mg/kg IV daily
- CrCl<10 mL/min: 1.25 mg/kg IV 3 times per week following hemodialysis

Conception and Contraception: Women of childbearing potential should use effective contraception during and for at least 30 days after treatment, men with partners of childbearing potential should be advised to use barrier contraception during and for at least 90 days after treatment. Ganciclovir may cause temporary or permanent inhibition of spermatogenesis—impaired fertility observed in animal studies.

Pregnancy: Avoid unless potential benefit outweighs risk—teratogenicity in animal studies.

Breastfeeding: Avoid—present in milk in animal studies.

Adverse effects: Common: diarrhea, upset stomach, nausea, vomiting, decreased appetite, dizziness, drowsiness, shaking (tremors), injection site reactions (pain, redness, or irritation), increased sweating, itching, decreased sperm production, or infertility

Notes: Monitoring requirements: Monitor full blood count closely (severe deterioration may require correction and possibly treatment interruption).

Ribavirin (Tribavirin)

ATC code: J05AB04

Injection for IV administration, 800 mg/10 mL phosphate buffer solution, LOU 4

Capsule, 200 mg, LOU 4

Indications and dose

Adult

Haemorrhagic fevers, oral: Initially 2 g, then 1 g every 6 hours for 4 days, then 500 mg every 6 hours for 6 days

Haemorrhagic fevers, by slow IV infusion (over 10–15 minutes): Initially 17 mg/kg (maximum, 1 g), then 17 mg/kg every 6 hours for 4 days, then 8 mg/kg (maximum, 500 mg) every 8 hours for 6 days

Haemorrhagic fever with renal syndrome, by slow IV infusion (over 10–15 minutes): Initially 33 mg/kg (maximum, 1 g), then 16 mg/kg (maximum, 1 g) every 6 hours for 4 days, then 8 mg/kg (maximum, 500 mg) every 8 hours for 6 days.

Paediatric

Haemorrhagic fevers, oral

Child all ages: Initially 30 mg/kg (maximum 2 g) then 15 mg/kg (maximum 1 g) every 6 hours for 4 days, then 7 mg/kg (maximum 500 mg) every 6 hours for 6 days

Haemorrhagic fevers, slow IV infusion

Child all ages: 17 mg/kg every 6 hours for 4 days, then 7 mg/kg every 8 hours for 6 days.

Precautions: Ribavirin is potentially mutagenic, tumour promoting and gonadotoxic. May cause birth defects and/or death of the exposed fetus. Both males and females should avoid pregnancy during treatment and for at least 6 months after treatment. Ribavirin causes anaemia, treatment with other drugs which also have this effect may worsen this, avoid combinations or monitor closely.

Renal impairment: Avoid use in all degrees of renal impairment.

Hepatic impairment: Dose reduction not necessary, avoid in severe hepatic dysfunction or decompensated cirrhosis.

Adverse effects: Common: Rash, pruritus, anorexia, dyspnoea, cough, anaemia, haemolytic anemia (patients with pre-existing cardiac disease are at increased risk), increase in uric acid concentration. Dizziness, insomnia, irritability, fatigue, depression, suicidal ideation (in combination with peginterferon alfa treatment (more frequent in children), thrombotic thrombocytopenic purpura, increases in serum bilirubin and liver enzymes, particularly AST and ALT. Rare: Reticulocytosis, MI, arrhythmias,

interstitial pneumonitis, pancreatitis, hypersensitivity. Other adverse effects: Neutropenia, aplastic anaemia, nausea, vomiting, diarrhoea, colitis, fever, rigors, myalgia, arthralgia, headache, impaired concentration, anxiety, autoimmune disorders, diabetes, hypothyroidism, hyperthyroidism, retinal haemorrhage, retinal thrombosis, alopecia.

Interactions with other medicines: Interactions with other medicines with ribavirin may occur for up to 2 months after stopping ribavirin due to its long half-life.

Azathioprine: increased risk of azathioprine induced myelotoxicity.

Didanosine: ribavirin with didanosine has resulted in didanosine toxicity, e.g., pancreatitis, lactic acidosis, avoid combination.

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs): ribavirin may inhibit activation of NRTIs (lamivudine, stavudine and zidovudine appear unaffected), monitor HIV RNA level closely and review NRTI treatment if this increases, seek specialist advice. Monitor closely for NRTI toxicity.

Warfarin: ribavirin may decrease warfarin's anticoagulant effect, monitor INR and increase warfarin dose if needed.

Notes: Oral ribavirin should be taken with food.

Valganciclovir (Valgancyclovir)

ATC code: J05AB14

Powder for oral liquid, 50mg/ml LOU 5

Tablet, 450 mg, LOU 5

Adult

Induction treatment of CMV retinitis in patients with AIDS, oral: 900 mg twice a day for 21 days, taken with food

» *Maintenance treatment, oral:* 900 mg once daily, taken with food; duration of maintenance treatment is on an individual basis

» **Note:** If retinitis worsens, repeat induction treatment; however, consideration should be given to the possibility of viral drug resistance.

Prevention of CMV disease in CMV negative who have received a solid organ transplant from a CMV-positive donor, oral: 900 mg once daily starting within 10 days post-transplantation and continuing until 100 days post-transplantation; prophylaxis may be continued until 200 days post-transplantation.

» **Elderly:** Dose should be according to serum creatinine levels.

- For males = $\frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (0.011 \times \text{serum creatinine [micromol/L]})}$

» For females = 0.85 × male value

CrCl (mL/min)	Induction dose of valganciclovir	Maintenance/prevention dose of valganciclovir
≥60	900 mg twice daily	900 mg once daily
40–59	450 mg twice daily	450 mg once daily
25–39	450 mg once daily	450 mg every two days
10–24	450 mg every two days	450 mg twice weekly
<10	Not recommended	Not recommended

Paediatric

Based on BSA and creatinine clearance (Clcr) derived from the Schwartz formula (ClcrS) calculated as below:

Schwartz creatinine clearance formula [ClCrS] (mL/min/1.73 m2) = k × height (cm)

Serum creatinine (mg/dL)

Where k = 0.45 for children <2 years; 0.55 for boys aged 2 years to <13 years and girls aged 2–16 years; and 0.7 for boys aged 13–16 years. Children >16 years, refer to adult dose above.

Prevention of CMV disease in CMV-negative children who have received a solid organ transplant from a CMV-positive donor, oral: once daily mg dose (7 × BSA × ClcrS [see Schwartz creatinine clearance formula above]) should start within 10 days post-transplantation and continue until 100 days post-transplantation. For kidney transplant patients, the recommended once daily dose (7 × BSA × ClcrS) should start within 10 days post-transplantation and continue until 200 days post transplantation.

Note: All calculated doses should be rounded off to the nearest 25-mg increment for the actual deliverable dose. The tablet should not be broken or crushed because it is considered a potential teratogen and carcinogen in humans. Avoid direct contact with skin and mucous membranes.

Precautions: Renal impairment, children, and the elderly.

- **Female of child-bearing age:** should be advised to use contraception at least for 30 after treatment.
- **Male patients:** should be advised to practice barrier contraception for at least 90 days following treatment.

Contraindications: Hypersensitivity to valganciclovir, ganciclovir and acyclovir, breastfeeding, pregnancy.

Renal impairment: Serum creatinine levels or estimated creatinine clearance should be monitored carefully. Dosage adjustment is required according to creatinine clearance, as shown in the table on previous page (under elderly dosing).

Hepatic impairment: Safety and efficacy not established.

Interactions:

- Valganciclovir is rapidly metabolized to ganciclovir which interacts with the following drugs
- Probenecid leading to reduced renal function. Avoid concomitant use.
- Imipenem-cilastatin: convulsions have been reported. Avoid concomitant use.
- Zidovudine: lead to neutropenia and anaemia. Avoid concomitant use.

Adverse effects: Very common: candida infections (oral candidiasis), neutropenia, decreased appetite, headache, cough, dyspnoea, diarrhoea, nausea, vomiting, abdominal pain, dermatitis, pyrexia, fatigue. Common: sepsis, influenza, urinary tract infection, cellulitis, thrombocytopenia, leukopenia, pancytopenia, hypersensitivity, weight decreased, depression, confusional, anxiety, insomnia, neuropathy peripheral, dizziness, paraesthesia, convulsion, dysgeusia, tremor, visual impairment, retinal detachment, vitreous floaters, eye pain, conjunctivitis, macular oedema, ear pain, hypotension, constipation, pancreatitis, elevated (alkaline phosphatase, AST and alanine aminotransferase), night sweats, pruritis, rash, muscle and back pain, muscle spasms, renal impairment, infertility in males. Uncommon: Bone marrow failure, agitation, tremor, deafness, dry skin, urticaria, chest pain

Notes:

- Caution in handling Valganciclovir is a potential teratogen and carcinogen. Manufacturer advises caution when handling the powder, reconstituted solution, or broken tablets and avoid inhalation of powder; if contact with skin or mucous membranes occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water.

7.4.4. Antihepatitis Medicines

7.4.4.1. Medicines for Hepatitis B

7.4.4.1.1. Nucleoside/Nucleotide reverse transcriptase inhibitors

Medicines for hepatitis B treatment should only be used under close supervision of a specialist

Entecavir

ATC code: J05AF10

Oral liquid, 0.05 mg/mL, LOU 5

Tablet, 0.5 mg, LOU 4

Indications and dose

Adult and adolescents ≥ 16 years

Chronic hepatitis B in patients with compensated liver disease (with evidence of viral replication and histologically documented active liver inflammation or fibrosis) not previously treated with nucleoside analogues, oral: 500 micrograms once daily

Chronic hepatitis B in patients with compensated liver disease (with evidence of viral replication and histologically documented active liver inflammation or fibrosis) and lamivudine-resistance, oral: 1 mg once daily, consider other treatment if inadequate response after 6 months

Chronic hepatitis B in patients with decompensated liver disease, oral: 1 mg once daily

Paediatric

Chronic hepatitis B

Child < 2 years: Safety and efficacy not established.

Child 16 years and above: Same as adults (see above)

Precautions: HIV infection—risk of HIV resistance in patients not receiving 'highly active ART'. Lamivudine-resistant chronic hepatitis B presents a risk of entecavir resistance. Discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

Renal impairment Consult product literature.
Dose adjustments: Reduce dose if eGFR less than 50 mL/min/1.73 m^2

Usual daily dose (0.5 mg)

- CrCl ≥50 mL/min: No dosage adjustment required
- CrCl 30–49 mL/min: Reduce to 0.25 mg/day or 0.5 mg every 48hrs
- CrCl 10–29 mL/min: Reduce to 0.15 mg/day or 0.5 mg every 72hrs
- CrCl <10 mL/min, hemodialysis, or CAPD: 0.05 mg/day or 0.5 mg every 7 days

Lamivudine-refractory/decompensated liver disease daily dose (1 mg)

- CrCl ≥50 mL/min: No dosage adjustment required
- CrCl 30–49 mL/min: Reduce to 0.5 mg/day or 1 mg every 48 hrs

- CrCl 10–29 mL/min: Reduce to 0.3 mg/day or 1 mg every 72 hrs
- CrCl <10 mL/min, hemodialysis, or CAPD: 0.1 mg/day or 1 mg every 7 days

Conception and contraception: Effective contraception required during treatment.

Pregnancy: Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk.

Breastfeeding: Manufacturer advises avoid—present in milk in animal studies.

Adverse effects: Common or very common: Diarrhoea, dizziness, drowsiness, dyspepsia, fatigue, headache, insomnia, nausea, vomiting. Uncommon: Alopecia, rash. Frequency not known: Lactic acidosis

Notes:

- **Monitoring requirements**: Monitor liver function tests every 3 months, and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).
- **Directions for administration**: To be taken on empty stomach at least 2 hours before or 2 hours after food.
- Oral solution should be used when needed for renal impairment dosage adjustments

Lamivudine (3TC)

ATC code: J05AF05

Tablet, 150 mg, LOU 4

Oral Liquid, 50 mg/5 mL, LOU 5

Indications and uses

Adult

Chronic hepatitis B infection either with compensated liver disease (with evidence of viral replication and histology of active liver inflammation or fibrosis) when first-line treatments cannot be used or (in combination with another antiviral drug without cross-resistance to lamivudine) with decompensated liver disease, oral: 100 mg once daily; patients receiving lamivudine for concomitant HIV infection should continue to receive lamivudine in a dose appropriate for HIV infection

Paediatric

Chronic hepatitis B infection either with compensated liver disease (with evidence of viral replication and histology of active liver inflammation or fibrosis) when first-line treatments cannot be used, or (in combination with another antiviral drug without cross-resistance to lamivudine) with decompensated liver disease, oral

Child 2–11 years: 3 mg/kg once daily (max. per dose 100 mg); children receiving lamivudine for concomitant HIV infection should continue to receive lamivudine in a dose appropriate for HIV infection

Child 12–17 years: 100 mg once daily: patients receiving lamivudine for concomitant HIV infection should continue to receive lamivudine in a dose appropriate for HIV infection

Precautions: Pancreatitis, renal impairment, chronic hepatitis B or C, hepatic disease.

Renal impairment: Moderate to severe: reduce dose.

Hepatic impairment: Dosage adjustment not required, use with caution in patients with decompensated liver disease. See notes in Precautions.

Adverse effects: Common: Headache, fatigue, nausea, anorexia, diarrhoea, skin rash, abdominal pain, pancreatitis (more commonly reported in children, up to 14%). Peripheral neuropathy, anaemia, decreased neutrophil count, increased liver enzymes, fat redistribution (see Lipodystrophy below), lactic acidosis, severe hepatomegaly with steatosis. **Lipodystrophy**: It has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (*indicates serious): *Emtricitabine: no information available, manufacturer advises to avoid concomitant use. *Interferon alfa: increased risk of hepatic toxicity. *Ribavirin: increased risk of hepatic toxicity. Sulfamethoxazole + trimethoprim: plasma concentration of lamivudine increased (avoid concomitant use of high dose sulfamethoxazole + trimethoprim).

Notes:

- Well tolerated. Can be given without regard to food.
- Store oral solution at room temperature. Use within 1 month of opening. Tablets may be crushed with a small amount of water or food and administered immediately.
- Also active against hepatitis B. Patients co-infected with HIV and hepatitis B should receive the HIV doses of lamivudine as above.

Tenofovir Alafenamide

ATC code: J05AF13

Tablet , 25 mg, LOU 4

Indications and dose

Adult

Chronic hepatitis B; 25mg once daily, taken with food (in combination with other anti-hepatitis B agents)

Paediatric

Chronic hepatitis B

Child 12–17 years: (above 35kg) 25mg once daily, taken with food (in combination with other anti-hepatitis B agents)

Contraindications: Hypersensitivity to tenofovir alafenamide, patients with galactose intolerance

Precautions: Patients with decompensated liver disease, Acute exacerbation of hepatitis b after treatment discontinuation,

Renal impairment: Not recommended in patients with creatinine clearance less than 15ml/min who are not receiving hemodialysis

Pregnancy: Maybe considered if necessary

Breastfeeding: It is unknown whether it is secreted in breast milk

Adverse effects: headache, nausea, fatigue, changes in lipid profile, dizziness, abdominal pain, abdominal distention, flatulence, increased ALT, rash, pruritis, angioedema, arthralgia, fatigue

Interactions with other medicines (*indicates serious): Carbamazepine, oxcarbamazepine, phenytoin, phenobarbitone, rifampicin, rifabutin, rifapentine, st john warts, itraconazole, ketoconazole, midazolam, sertraline, sofosbuvir, atanzanair, darunavir, lopinavir

Tenofovir Disoproxil Fumarate (TDF)

ATC code: J05AF07

Tablet, 300 mg (equivalent to 245 mg of tenofovir disoproxil), LOU 4

Indications and dose

Adult

Chronic hepatitis B infection with compensated liver disease (with evidence of viral replication and histologically documented active liver inflammation or fibrosis), oral: 245 mg once daily

Chronic hepatitis B infection with decompensated liver disease, oral: 245 mg once daily

Paediatric

Chronic hepatitis B infection with compensated liver disease (with evidence of viral replication and histology of active liver inflammation or fibrosis), oral

Child 12–17 years (body weight 35 kg and above): 245 mg once daily

Hepatic impairment: manufacturer advises caution in decompensated hepatic disease (limited information available).

Renal impairment: Dose adjustment in adults:

- eGFR 30–50 mL/min/1.73 m^2: 245 mg every 2 days
- eGFR 10–30 mL/min/1.73 m^2: 245 mg every 3–4 days

Adverse effects: Common or very common: Abdominal distension. Uncommon: Proximal renal tubulopathy. Rare or very rare: Acute tubular necrosis nephritis, nephrogenic diabetes insipidus renal impairment

Interactions with other medicines: Ciclosporin, didanosine, Eltrombopag, HIV-protease inhibitors (atazanavir, darunavir, lopinavir), Ledipasvir (with sofosbuvir), Leflunomide, Teriflunomide, Velpatasvir, Voxilaprevir.

Notes: Monitoring requirements:

- Test renal function and serum phosphate before treatment, then every 4 weeks (more frequently if at increased risk of renal impairment) for 1 year and then every 3 months, interrupt treatment if renal function deteriorates or serum phosphate decreases.
- Monitor liver function tests every 3 months and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).
- If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

7.4.4.2. Medicines for Hepatitis C

7.4.4.2.1. Non-pangenotypic direct-acting antiviral combinations

Ledipasvir + Sofosbuvir

ATC code: J05AP51

Tablet, 90 mg + 400 mg, LOU 5

Indications and dose

Adult

Chronic (long-lasting) hepatitis C genotypes 1, 4, 5, or 6 infections, oral: One tablet (90 mg/400 mg) daily for 12 weeks

Genotype	Description	Child-Pugh classification	Duration of treatment
1	Naïve without cirrhosis or with compensated cirrhosis	A	12 weeks, may consider 8 weeks in naïve patients without cirrhosis
	Resistance to PEG interferon alfa + ribavirin Without cirrhosis		12 weeks
	Treatment experienced, with compensated cirrhosis		24 weeks; may also a dd daily weight-based ribavirin
	Treatment naïve, treatment experienced With decompensated cirrhosis, including patients who have undergone liver transplantation	B or C	12 weeks in c ombination with ribavirin
1 or 4	Treatment naïve, treatment experienced Without cirrhosis or with compensated cirrhosis, including patients who have undergone liver transplantation	A	12 weeks in combination with ribavirin
4, 5, or 6	Treatment naïve, treatment experienced Without cirrhosis or with compensated cirrhosis	A	12 weeks

Paediatric

Hepatitis C virus (HCV) genotype 1, 4, 5, or 6 infection, oral

Child <3 years: Safety and efficacy not established

Child≥3 years and <17 kg: 33.75 mg/150 mg sachet of granules daily

Child ≥3 years and 17 to <35 kg: 45 mg/200 mg once daily

Child ≥3 years and ≥35 kg: 90 mg/400 mg once daily

Note: Duration of paediatric is same as adults.

Contraindications: Pregnancy and breastfeeding. If co-administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen.

Black Box Warnings:

Test all patients for evidence of current or prior HBV infection before initiating treatment with HCV direct acting antivirals (DAAs).

HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with DDAs and were not receiving HBV antiviral therapy

Some cases have resulted in fulminant hepatitis, hepatic failure, and death

Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up

Initiate appropriate patient management for HBV infection as clinically indicated

Interactions: Avoid concomitant use in patient on carbamazepine, fosphenytoin, oxycarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort, colchicine, topotecan.
Adverse effects: Very common: asthenia, fatigue, headache, cough. Common: nausea, diarrhoea, dizziness, dyspnoea, insomnia, increased bilirubin, increased lipase, myalgia, irritability. Rare: asymptomatic creatine kinase elevation, Grade ¾

7.4.4.2.2.Pangenotypic direct-acting antiviral combinations

Sofosbuvir+Velpatasvir

ATC code: J05AP55

Tablet , 400/100mg, LOU 5

Indications and dose

Adult

Chronic hepatitis C infection: 400/100 mg once daily for 12 weeks (may extend to 24 weeks in some circumstances)

Paediatric

Chronic hepatitis C infection

Child 3–17 years: 17-30kg; 250/50mg once daily for 12 weeks

Child 3–17 years: above 30kg; 400/100 mg once daily for 12 weeks

Contraindications: Hypersensitivity to Sofosbuvir/Velpatasvir, medicinal products that are p glycoprotein and CYP450 inducers

Precautions: Risk of reactivation of hepatitis B virus, cross resistance with other ns5A inhibitors

Hepatic impairment: No dose adjustment required

Renal impairment: No dose adjustment required for patients with mild or moderate renal impairment.

Pregnancy: Limited data on use of Sofusbuvir/Velpatasvir in pregnant women

Breastfeeding: Unknown

Adverse effects: Hypoglycemia, headache, fatigue, nausea, vomiting, rash, angioedema, SJS.

Interactions with other medicines: Amiodarone, Tenofovir, carbamazepine, phenobarbitone, phenytoin, efavirenz, modafinil, oxcarbazepine, rifapentine, vitamin K antagonists, calcineurin inhibitors, famotidine, cimetidine, omeprazole, amiodarone, digoxin, dabigatran, ketoconazole, voriconazole, tenofovir, lopinavir, raltegravir, atorvastatin, methadone, cyclosporin, oral contraceptives

7.5. Antiprotozoal Medicines

7.5.1. Antiamoebic and Antigiardiasis Medicines

Diloxanide

ATC code: P01AC01

Tablet, 500 mg (furoate), LOU 2

Indications and dose

Adult

Amoebiasis (asymptomatic carriers in non-endemic areas, eradication of residual luminal amoebae after treatment of invasive disease with other drugs), oral: 500 mg three times daily for 10 days

Paediatric

Amoebiasis, oral

Child over 25 kg: 7 mg/kg (maximum 500 mg) three times daily for 10 days; course of treatment may be repeated if necessary

Contraindications: Pregnancy (defer treatment until after first trimester).

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common: flatulence. Vomiting, pruritus and urticaria.

Interactions with other medicines: There are no known interactions where it is recommended to avoid concomitant use.

Notes:

» Diloxanide is not effective against hepatic

amoebiasis, but a 10-day course should be given at the completion of metronidazole or tinidazole treatment to destroy any amoebae in the gut.

» Treatment with diloxanide is regarded as successful if stools are free of Entamoeba histolytica for 1 month. Several stool specimens should be examined when evaluating response to treatment.

» WHO age/weight restriction: > 25 kg weight.

Diloxanide Furoate + Metronidazole

ATC code: Not assigned

Oral liquid, 250 mg + 200 mg, LOU 2

Tablet, 500 mg + 400 mg, LOU 2

Indications and dose

Adult

Acute amoebiasis, chronic amoebiasis, hepatic amoebiasis, and other systemic diseases due to E. histolytica, giardiasis, oral: One tablet (500 mg + 400 mg) three times daily for 5–10 days

Paediatric

Acute amoebiasis, chronic amoebiasis, hepatic amoebiasis, and other systemic diseases due to E. histolytica, giardiasis, oral

Child all ages:

Based on: Metronidazole: 25mg/kg/day + diloxanide furoate 20mg/kg/day in divided doses for 5–10days

Adverse effects: Nausea, dryness in mouth, metallic taste, flatulence, anorexia, vertigo, ototoxicity, abdominal distress.

Metronidazole

ATC code: P01AB01

Injection, 500 mg in 100-mL vial, LOU 3

Oral liquid, 200 mg/5 mL (as benzoate), LOU 2

Tablet (scored), 400 mg, LOU 2

Indications and dose

Adult

Giardiasis, oral: 2g once daily for 3 days or 400 mg three times daily for 5 days

Amoebiasis (intestinal infection), oral: 800 mg three times daily for 5 days

Amoebiasis (extra-intestinal infection), oral: 400-800 mg three times daily for 5-10 days. Alternatively, 35-50 mg /kg daily in 3 divided doses for 5-10 days. Maximum: 2,400 mg daily.

Invasive amoebiasis (if oral administration not possible), by IV infusion: 30 mg/kg daily in 3 divided doses (until patient able to complete course with oral drugs), subsequent course of luminal amoebicide

Urogenital trichomoniasis, oral: 2g as a single dose or 400 mg twice daily for 7 days; sexual partners should be treated concomitantly.

Paediatric

Giardiasis, oral

Child 1-3 years: 50 mg once daily for 3 days.

Child>3-7 years: 600-800 mg once daily for 3 days;

Child>7-10 years: 1g once daily for 3 days.

Child >10 years: Same as adult dose.

Alternative paediatric dosing: 15mg/kg/day in divided doses for 5 to 10 days

Amoebiasis, oral

Infant or child: 30mg/kg/day in 3 divided doses for 8 to 10 days

Amoebiasis, by IV

Infant or child: 30mg/kg/day in 3 divided doses for 8 to 10 days

The IV route should only be used if oral administration is not possible and only until the patient can complete the course orally.

Precautions: Hepatic impairment, disulfiram-like reaction with alcohol consumption, clinical and laboratory monitoring (including full blood count and hepatic function tests) in courses lasting longer than 10 days. Skilled tasks: Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Renal impairment: Metabolites may accumulate in severe impairment possibly causing adverse effects. Dose adjustment is not usually necessary.

Hepatic impairment: Severe impairment: reduce total daily dose to one third and give once daily. Use with caution in hepatic encephalopathy

Adverse effects: Common: GI intolerance (nausea, abdominal pain, vomiting, diarrhoea), anorexia, metallic taste, CNS effects (e.g., dizziness, headache), thrombophlebitis (if administered intravenously). Furry tongue, glossitis, stomatitis, paraesthesia. Rare: Pancreatitis, abnormal liver function tests, jaundice, hepatitis, optic neuritis, thrombocytopenia, CDAD, hypersensitivity reactions (e.g., rash, itch, flushing, fever), anaphylaxis, angioedema, erythema multiforme, SJS, leukopenia, peripheral neuropathy, seizures, darkening of the urine.

Interactions with other medicines (*indicates serious):

Mebendazole: increased levels/effect of metronidazole.

Phenobarbital: metabolism of metronidazole accelerated (reduced plasma concentration).

Phenytoin: metabolism of phenytoin inhibited (increased plasma phenytoin concentration).

Typhoid vaccine: reduced effectiveness of vaccine.

Warfarin: enhanced anticoagulant effect.

Notes:

» Well absorbed orally and the IV route is normally reserved for severe infections or those unable to take or tolerate oral medication.

» Oral absorption from the suspension is lower than from the tablets.

» Patient advice Metronidazole tablets should be swallowed whole with water, during or after

a meal, metronidazole suspension should be taken 1 hour before a meal.

» Administration For IV infusion, infuse over 20–30 minutes.

» In amoebiasis and giardiasis, various dosage regimens are used and definitive recommendations should be based on local experience. Eradication may take re-treatment and longer courses.

Tinidazole

ATC code: P01AB02

Tablet (f/c), 250 mg, 500 mg, LOU 2

Indications and dose

Adult

Anaerobic infections, oral: Initially 2 g, followed by 1 g daily usually for 5–6 days; alternatively, 500 mg twice daily usually for 5–6 days

Bacterial vaginosis, acute ulcerative gingivitis, oral: 2 g for 1 single dose

Abdominal surgery prophylaxis oral: 2 g for 1 single dose, to be administered approximately 12 hours before surgery

Intestinal amoebiasis, oral: 2 g daily for 2–3 days

Amoebic involvement of the liver, oral: 1.5–2 g once daily for 3–6 days

Urogenital trichomoniasis, giardiasis, oral: 2 g for 1 single dose

Helicobacter pylori eradication, oral: 2 g for 1 single dose, may be repeated once if necessary

Paediatric

Intestinal amoebiasis, oral

Child 1 month–11 years: 50–60 mg/kg once daily (max. per dose 2 g) for 3 days

Child 12–17 years: 2 g once daily for 2–3 days

Amoebic involvement of liver, oral

Child 1 month–11 years: 50–60 mg/kg once daily (max. per dose 2 g) for 5 days

Child 12–17 years: 1.5–2 g once daily for 3–6 days

Urogenital trichomoniasis, giardiasis, oral

Child 1 month–11 years: 50–75 mg/kg (max. per dose 2 g) for 1 single dose, may be repeated once if necessary

Child 12–17 years: 2 g for 1 single dose, may be repeated once if necessary

Pregnancy: manufacturer advises avoid in first trimester.

Breastfeeding: present in milk—manufacturer advises avoid breastfeeding during and for 3 days after stopping treatment.

Adverse effects: Common or very common: Abdominal pain, appetite decreased, diarrhoea, headache, nausea, skin reactions, vertigo, vomiting. Frequency not known: Angioedema, ataxia, dizziness, fatigue, flushing, leucopenia, oral disorders, peripheral Neuropathy, seizure, sensation abnormal, taste altered, tongue discolouration, urine discolouration.

Interactions with other medicines: Alcohol (beverage) potentially causes a disulfiram-like reaction when given with tinidazole - Avoid for 72 hours stopping treatment. Tinidazole is predicted to increase the anticoagulant effect of coumarins - Monitor INR and adjust dose.

Notes: Monitoring requirements: clinical and laboratory monitoring advised if treatment exceeds 10 days.

7.5.2. Antileishmaniasis Medicines

Amphotericin B

ATC code: J02AA01

Injection, 50 mg liposomal in vial, LOU 4

Indications and dose

Adult and child

Visceral and mucocutaneous leishmaniasis (unresponsive to antimonial compounds), by IV infusion: 3 - 5 mg/kg/dose once daily for 6 to 10 days up to a total dose of 30 mg/kg

Note: In Kenya Liposomal Amphotericin B is recommended as second line treatment except in the following conditions where it is recommended as first line:

» Pregnant women

» Severely ill patients

» Children less than two years old and adults over 45 years

» Leishmania – HIV coinfected patients

» Contraindication to sodium stibogluconate or Paromomycin treatment

Contraindications: Hypersensitivity, renal impairment

Precautions: renal impairment, myocardial toxicity, avoid rapid infusion (risk of arrhythmias), neutropenic patients, liposomal amphotericin B: diabetes as each 50 mg vial of liposomal amphotericin B contains 900 mg of sucrose

Test dose:

Liposomal amphotericin B: Initial test dose 100 micrograms/kg (maximum 1 mg) infused intravenously over 10 minutes.

Renal impairment: Not recommended.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Adverse effects are similar for all amphotericin B formulations, the rates depend on the formulation used, the liposomal formulation is generally better tolerated.

Common: Fever, headache, nausea and vomiting, anorexia, diarrhoea, epigastric pain, muscle and joint pain, thrombophlebitis, anaemia, nephrotoxicity. Hypotension or hypertension, hypokalaemia, hypomagnesaemia, cardiac arrest, arrhythmias (rapid infusion of conventional amphotericin B), blood dyscrasias, GI bleeding, elevated liver enzymes, hepatotoxicity, rash, neurological effects (e.g., seizures, confusion, blurred vision, hearing loss, tinnitus). Rare: Anaphylactoid reactions, hyperkalaemia (especially in renal impairment), cardiovascular toxicity (including arrhythmias, ECG changes).

changes are dose related and generally reversible (except with cumulative doses > 3–5 g). Distal tubular damage may lead to loss of concentrating ability, renal

tubular acidosis, nephrocalcinosis, hypokalaemia and hypomagnesaemia. Anuria or oliguria may occur. Risk is greater in those with renal impairment or when used with other nephrotoxic drugs. Nephrotoxicity may be associated with sodium depletion.

Liposomal amphotericin B is less nephrotoxic than conventional (deoxycholate) amphotericin B.

With liposomal amphotericin B, one or more acute infusion reactions (chest pain, hypoxia, dyspnoea, severe abdominal, flank or leg pain, flushing and urticaria) may occur, these may be related to the liposomal component, frequency is very variable.

Interactions with other medicines

Aminoglycosides including paromomycin, vancomycin etc: increased risk of nephrotoxicity.

Foscarnet: increased risk of nephrotoxicity.

Sodium stibogluconate: Increased risk of cardiotoxicity.

Bupropion: Increased risk of seizure

Notes:

- Check renal function before starting treatment,
- Prophylactic antipyretics or hydrocortisone should only be used in patients who have previously experienced acute adverse reactions (in whom continued treatment with amphotericin B is essential).
- Proper hydration and potassium supplementation are important. Treatment should always be given in hospital to enable continuous monitoring of patients.
- Liposomal amphotericin B Reconstitute as per product instructions including filtering through a 5-micron filter and further dilute with glucose 5% to produce a final concentration of 0.2–2 mg/mL.
- Initial test dose should be given over 10 minutes. Then infuse subsequent doses over 30–60 minutes.

Paromomycin

ATC code: A07AA06

Injection solution (IM), 375 mg/mL (as sulphate) in 2-mL amp, LOU 4

Indications and dose

Adult

Visceral leishmaniasis (in combination with antimonial compounds), by IM: 11 mg/kg daily for 21 days

Intestinal amebiasis, oral: 25 – 35 mg/kg/day in 3 divided doses for 5–10 days

Paediatric

All doses are in terms of paromomycin base.

Visceral leishmaniasis in the Indian subcontinent, by IM

Child over 5 kg: 11 mg/kg daily for 21 days.

Visceral leishmaniasis in East Africa (only use in combination with pentavalent antimonials), IM

Child over 5 kg: 11 mg/kg daily for 17 days

Contraindications: Intestinal obstruction, hypersensitivity to paromomycin or aminoglycosides

Precautions: Impaired GI motility, possible or proven ulcerative bowel lesions, impaired renal function, Superinfection in prolonged use.

Renal impairment: Mild: avoid or use with caution, nephrotoxic.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common: Nausea, vomiting, diarrhoea, abdominal cramps, allergic reaction, injection site pain, fever. Uncommon: Rash, headache, dizziness, anorexia, reversible ototoxicity, steatorrhoea liver enzymes, renal toxicity.

Interactions with other medicines: There are no know significant Interactions with other medicines. Possible cross-reactivity with aminoglycosides

Notes: Administer with meals

Sodium Stibogluconate or Meglumine Antimoniate

ATC code: P01CB01, P01CB02

Doses are expressed as mg of pentavalent antimony

Injection, 100 mg/mL (100-mL vial), LOU 4

Sodium stibogluconate IV/IM injection: 100 mg of pentavalent antimony per mL, LOU 4

Indications and dose

Adult

Visceral, cutaneous, mucocutaneous and post-kala-azar dermal leishmaniasis (in combination with paromomycin or as monotherapy where paromomycin is not available or is contraindicated), by IM, IV: 20 mg/kg daily for 20 days or 28 days for HIV patients; if relapse, retreat immediately with same daily dosage

Cutaneous leishmaniasis, by intralesional injection: 1–3 mL into base of lesion; if no apparent response, may be repeated once or twice at intervals of 1–2 days; relapse is unusual

Paediatric

Doses are expressed as mg of pentavalent antimony.

Sodium stibogluconate IV/IM injection contains 100 mg pentavalent antimony per mL.

Meglumine antimoniate IV/IM injection contains 81 mg pentavalent antimony per mL.

Visceral leishmaniasis, IV/IM

Child all ages: 20 mg/kg (minimum 200 mg) daily for 28 days in *L. infantum* infections and for 30 days in *L. donovani* infections

Post-kala-azar dermal leishmaniasis, IV/IM

Child all ages: 20 mg/kg (minimum 200 mg) daily for 30–60 days

Mucocutaneous leishmaniasis, IM/IV

Child all ages: 20 mg/kg daily for 30 days

Systemic treatment is acceptable if the patient suffers from numerous lesions (typically >4), face-disfiguring or complicated lesions, if the size or localization of the lesion makes local therapy impossible, or if local therapy has been tried and failed. For diffuse cutaneous forms by L. aethiopica, the addition of paromomycin may be necessary.

Contraindications: Pre-existing severe cardiac, liver, renal, pancreas or haematological morbidities.

Precautions: Renal impairment, hepatic impairment, altered cardiac conduction

Renal impairment: Not recommended

Hepatic impairment: Not recommended – elevates hepatic enzymes

Pregnancy: Not recommended

Breastfeeding: Not recommended – excreted in milk

Adverse effects: Common: Anorexia, vomiting, nausea, abdominal pain, pain on IM injection site. Frequency not defined: malaise, myalgia, arthralgia, headache, metallic taste, lethargy, elevated pancreatic and liver enzymes, leukopenia, anaemia, thrombocytopenia, pneumonia. Rare: Cardiotoxicity, T-wave inversion, prolonged QT interval and arrhythmias, hepatotoxicity, pancreatitis, flushing, bleeding from nose or gum, vertigo, fever, sweating, rash, anaphylaxis, pain and thrombosis on IV administration, renal impairment and/or damage, peripheral neuropathy, substernal pain or cough.

Interactions with other medicines:

Amphotericin B: possibly increased risk of fatal cardiac arrhythmias.

QT-Prolonging agents, e.g., Chloroquine, Domperidone (high risk): possibly increased risk of Cardiotoxicity

Notes:

Administration:

- The injection should be filtered immediately before administration using a 5 micron or less filter. IV injection should be given either by infusion (over 5–10 minutes) or slow injection through a fine needle (23–25 gauge, 0.6–0.5 mm) to avoid any risk of subsequent thrombosis. infusions should be ceased if coughing or substernal pain occurs.
- IM injection should be given deep into the muscle. If the volume of injection exceeds a suitable size for the patient, it may be painful it therefore should be divided into two doses, one in each buttock or thigh.
- Sodium stibogluconate and meglumine antimoniate are not the same compound. Please ensure doses are calculated on the compound available.
- To be used in combination with paromomycin

7.5.3. Antimalarial Medicines

7.5.3.1. For curative treatment

Medicines for the treatment of P. falciparum malaria cases should be used in combination according to treatment guidelines

Artemether

ATC code: P01BE02

Injection (oily, IM), 80 mg/mL in 1-mL amp, LOU 2

Indications and dose

Adult

Severe P. falciparum malaria, by IM injection: Loading dose of 3.2 mg/kg, then 1.6 mg/kg daily until patient can tolerate oral medication or up to a maximum of 7 days; this is followed by a single dose of oral mefloquine 15 mg/kg (occasionally, 25 mg/kg if necessary) to effect a radical cure.

Paediatric

Severe P. falciparum malaria in areas of quinine resistance, IM injection

Infant or child over 6 months: Loading dose of 3.2 mg/kg, then 1.6 mg/kg daily until patient can tolerate oral medication or to maximum of 7 days; this is followed by a complete treatment course of an effective artemisinin-based combination therapy to effect a radical cure.

Contraindications: First trimester of pregnancy.

Precautions: Skilled tasks: Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Renal impairment: Caution in severe impairment, monitor ECG and plasma potassium.

Hepatic impairment: Caution in severe impairment, monitor ECG and plasma potassium.

Adverse effects: Common: Headache, nausea, vomiting, abdominal pain, diarrhoea, dizziness, tinnitus. Uncommon: Neutropenia, elevated liver enzyme values. Rare: Cardiotoxicity (after high doses), neurotoxicity in animal studies.

Interactions with other medicines (*indicates serious):

- *Amitriptyline: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- *Azithromycin: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- *Chloroquine: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- *Chlorpromazine: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- *Ciprofloxacin: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- *Erythromycin: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- *Fluconazole: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- *Fluoxetine: avoid concomitant use.
- *Grapefruit juice: metabolism of artemether and lumefantrine may be inhibited (avoid concomitant use).
- Haloperidol: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- Lopinavir: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- Mefloquine: manufacturer of artemether with

lumefantrine advises avoid concomitant use.

- Ofloxacin: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- Primaquine: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- Proguanil: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- Pyrimethamine: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- Quinine: risk of ventricular arrhythmias (manufacturer of artemether with lumefantrine advises avoid concomitant use).
- Ritonavir: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- Saquinavir: manufacturer of artemether with lumefantrine advises avoid concomitant use.
- Sulfadoxine + pyrimethamine: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Notes:

- Administration: Since small volumes are required for children, a 1 mL syringe should be used to ensure correct dosage.
- Oily injection currently formulated in arachis (peanut) oil. Care should be taken in patients with known peanut allergy.

Artemether + Lumefantrine (AL)

ATC code: P01BE52

Tablet, 20 mg/120 mg, LOU 1

Tablet (dispersible, 20 mg/120 mg, LOU 1

Indications and dose

Adult

Uncomplicated falciparum malaria, oral: Initially 4 tablets followed by 5 further doses of 4 tablets each at 8, 24, 36, 48, and 60 hours (total, 24 tablets over 60 hours)

Paediatric

Uncomplicated P. falciparum and other Plasmodium malaria, oral

Infant or child 5–14 kg: Initially 1 tablet followed by 5 further doses of 1 tablet each at 8, 24, 36, 48, and 60 hours (total 6 tablets over 60 hours)

Child 15–24 kg: Initially 2 tablets followed by 5 further doses of 2 tablets each at 8, 24, 36, 48, and 60 hours (total 12 tablets over 60 hours)

Child 25–34 kg: Initially 3 tablets followed by 5 further doses of 3 tablets each at 8, 24, 36, 48, and 60 hours (total 18 tablets over 60 hours)

Child over 34 kg: Initially 4 tablets followed by 5 further doses of 4 tablets each at 8, 24, 36, 48, and 60 hours (total 24 tablets over 60 hours)

Weight	Age	# of tablets	Dose to be administered at 0, 8, 24, 36, 48, and 60 hours
5 to 15 kg	<3 years	1	20 mg artemether + 120 mg lumefantrine
15 to <25 kg	3 to <8 years	2	40 mg artemether + 240 mg lumefantrine
25 to <35 kg	8 to <12 years	3	60 mg artemether and 360 mg lumefantrine
≥35 kg	≥12 years	4	80 mg artemether and 480 mg lumefantrine

Contraindications: First trimester of pregnancy, history of arrhythmias, history of clinically relevant bradycardia, history of congestive heart failure accompanied by reduced left ventricular ejection fraction, family history of sudden death or of congenital prolongation of QTc interval (also see Precautions).

Precautions: Electrolyte disturbances, concomitant administration of drugs that prolong QT interval, monitor patients unable to take food (greater risk of recrudescence), severe renal impairment or hepatic impairment.

Renal impairment: Severe: caution, monitor ECG and plasma potassium.

Hepatic impairment: Severe: caution, monitor ECG and plasma potassium.

Adverse effects: Common: Abdominal pain, anorexia, diarrhoea, nausea and vomiting, headache, dizziness, sleep disorders, palpitation, arthralgia, myalgia, cough, asthenia, fatigue, pruritus, rash. Infrequent: Paraesthesia, ataxia. Rare: Hepatitis, hypersensitivity.

Interactions with other medicines (*indicates serious):

Amitriptyline: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Azithromycin: manufacturer of AL advises avoid concomitant use.

Chloroquine: manufacturer of AL advises avoid concomitant use.

Chlorpromazine: manufacturer of AL advises avoid concomitant use.

Ciprofloxacin: manufacturer of AL advises avoid concomitant use.

Erythromycin: manufacturer of AL advises avoid concomitant use.

Fluconazole: manufacturer of AL advises avoid concomitant use.

Fluoxetine: avoid concomitant use.

Grapefruit juice: metabolism of AL may be inhibited (avoid concomitant use

Haloperidol: manufacturer of AL advises avoid concomitant use.

Levofloxacin: manufacturer of AL advises avoid concomitant use.

Lopinavir: manufacturer of AL advises avoid concomitant use.

Mefloquine: manufacturer of AL advises avoid concomitant use.

Ofloxacin: manufacturer of AL advises avoid concomitant use.

Primaquine: manufacturer of AL advises avoid concomitant use.

Proguanil: manufacturer of AL advises avoid concomitant use.

Pyrimethamine: manufacturer of AL advises avoid concomitant use.

Quinine: risk of ventricular arrhythmias (manufacturer of AL advises avoid concomitant use).

Ritonavir: manufacturer of AL advises avoid concomitant use.

Saquinavir: manufacturer of AL advises avoid concomitant use.

Sulfadoxine + pyrimethamine: manufacturer of AL advises avoid concomitant use.

Notes:

- Non-dispersible tablets may be crushed.
- If the dose is vomited within 1 hour of taking, the dose should be repeated; this is a particular risk in children.

Artesunate

ATC code: P01BE03

Injection: ampoules, containing 60 mg anhydrous artesunic acid with a separate amp of 5% sodium bicarbonate solution, LOU 2

Injection (IM/IV), 30-mg vial and 60-mg vial, LOU 2

Suppository, 100 mg, LOU 1

Indications and dose

Adult

Severe malaria, IV or IM: Initially 2.4 mg/kg, then repeat at 12-hour intervals for 2 further doses, then once daily

Paediatric

Severe malaria, IV, IM, Rectal suppository

IV, IM

child <20kg: 3.0 mg/kg

child >20kg: 2.4 mg/kg given at 0, 12, and 24 hours, then once daily until oral treatment is possible (NB: Give a full course of artemisinin-based combination therapy [see artemether + lumefantrine] or oral quinine after initial parenteral artesunate).

Rectal suppository

Child 2 months–3 years(5-14kg): 100mg suppository

Child >3–6 years: 200mg (two 100mg suppositories) suppositories

Contraindications: First trimester of pregnancy.

Precautions: Risk of recurrence if used as oral monotherapy in non-immune patients. Skilled tasks: warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike or operating machinery, for 24 hours

Renal impairment: No information available.

Hepatic impairment: No information available.

Adverse effects: Common: Headache, nausea, vomiting, convulsions, abdominal pain, diarrhoea, dizziness, tinnitus. Uncommon: Neutropenia, elevated liver enzyme values. Rare: ECG abnormalities, including prolongation of QT interval, temporary suppression of reticulocyte response and induction of blackwater fever reported, neurotoxicity in animal studies.

Interactions with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

- Artesunate monotherapy is not recommended for uncomplicated malaria due to the risk of developing drug resistance.
- Reconstitution of parenteral forms:
- Artesunic acid should be dissolved in 1 mL of sodium bicarbonate 5% solution for injection (to form sodium artesunate). This can be administered intramuscularly or then further diluted in 5 mL of glucose 5% solution for injection before IV administration by bolus injection. Solutions should be freshly prepared prior to administration, consult manufacturer's literature.
- Artesunate suppository is recommended for antimalarial treatment as a 10mg/kg body weight single dose while the patient is being transferred to the nearest hospital.

Artesunate + Pyronaridine Tetraphosphate

ATC code: P01BF06

Tablet (f/c), 60 mg + 180 mg, LOU 2

Granules for oral suspension, 20 mg + 60 mg, LOU 2

Indications and dose

Adult

Uncomplicated malaria (P. falciparum and P. vivax), oral

- **Body weight 24 kg– <45 kg:** 2 tablets daily for 3 days
- **Body weight 45 kg– <65 kg:** 3 tablets daily for 3 days
- **Body weight >65 kg:** 4 tablets daily for 3 days

Paediatric

Body weight 20 kg– <24 kg: 1 tablet daily for 3 days

Contraindications: hypersensitivity to active ingredients and excipients, renal and hepatic impairment

Precautions: monitor the renal and liver functions in the elderly population.

Adverse effects: anaemia, bradycardia, neutropenia, abdominal pain, vomiting.

Interactions with other medicines: Increased with fatty food and this may cause severe adverse effects such as an irregular heart rhythm in some patients. Take this medicine on an empty stomach.

Notes:

- In the event of vomiting within 30 minutes of administration after the first dose, a repeat dose should be given. Appropriate dose adjustments or replacement with suitable alternative may be necessary based on clinical condition.
- Not for use in children weighing <5 kg. A granule formulation is available for children between 5 kg to 20 kg.

Dihyrodroartemisin + Piperaquine (DHA-PPQ)

ATC code: P01BF05

Tablet, 20 mg + 160 mg, LOU 3

Tablet (scored), 40 mg + 320 mg, LOU 3

Indications and dose

Adult

Uncomplicated falciparum, oral

- **Body weight 36–74 kg**: 3 tablets once daily for 3 days, max. 2 courses in 12 months, second course given at least 2 months after first course
- **Body weight 75–99 kg**: 4 tablets once daily for 3 days, max. 2 courses in 12 months, second course given at least 2 months after first course

Paediatric

Second-line treatment of uncomplicated falciparum malaria, oral

Child 6 months–17 years (body weight 7–12 kg): 0.5 tablet once daily for 3 days, max. 2 courses in 12 months, second course given at least 2 months after first course

Child 6 months–17 years (body weight 13–23 kg): 1 tablet once daily for 3 days, max. 2 courses in 12 months, second course given at least 2 months after first course

Child 6 months–17 years (body weight 24–35 kg): 2 tablets once daily for 3 days, max. 2 courses in 12 months, second course given at least 2 months after first course

Child 6 months–17 years (body weight 36–74 kg): 3 tablets once daily for 3 days, max. 2 courses in 12 months, second course given at least 2 months after first course

Child 6 months–17 years (body weight 75–99 kg): 4 tablets once daily for 3 days, max. 2 courses in 12 months, second course given at least 2 months after first course

Dihyrodroartemisin + piperaquine (DHA-PPQ): Summary of dosing according to weight bands, given daily for 3 days

Body weight (kg)	DHA-PPQ (mg)
5 to <8	20 + 160
8 to <11	30 + 240
11 to <17	40 + 320
17 to <25	60 + 480
25 to <36	80 + 640
36 to <60	120 + 960
60 to <80	160 + 1280
>80	200 + 1600

Contraindications: Acute MI, bradycardia, congenital long QT syndrome, electrolyte disturbances, family history of sudden death, heart failure with reduced left ventricular ejection fraction, history of symptomatic arrhythmias, left ventricular hypertrophy, risk factors for QT interval prolongation, severe hypertension.

Pregnancy: Teratogenic in animal studies—manufacturer advises use only if other antimalarials cannot be used.

Breastfeeding: Manufacturer advises avoid—present in milk in animal studies.

Hepatic impairment: Manufacturer advises caution in jaundice or in moderate to severe failure (no information available)—monitor ECG and plasma potassium concentration.

Monitoring Manufacturer advises monitor ECG and plasma-potassium concentration in moderate to severe hepatic impairment.

Renal impairment No information available in moderate to severe impairment.

Adverse effects: Common or very common: Anaemia, arrhythmias (in adults), asthenia, conjunctivitis (in children), eosinophilia, fever, headache (in children), leucocytosis (in children), leucopenia (in children), neutropenia (in children), QT interval prolongation, thrombocytopenia (in children). Uncommon: Abdominal pain (very common in children). appetite decreased (very common in children), arthralgia, cardiac conduction disorder, cough (very common in children), diarrhoea (very common in children), dizziness (in adults), epistaxis (in children), hepatic disorders, hypochromia (in children), increased risk of infection (very common in children), lymphadenopathy (in children), myalgia (in adults), nausea, rhinorrhoea (in children), seizure, skin reactions (very common in children), splenomegaly (in children), stomatitis (in children), thrombocytosis (in children), vomiting (very common in children)

Interactions with other medicines: St John's Wort is predicted to decrease the concentration of antimalarials (piperaquine) – Avoid.

Note: Monitoring requirements:

- Consider obtaining ECG in all patients before third dose and 4–6 hours after third dose. If QTC interval more than 500 milliseconds, discontinue treatment and monitor ECG for a further 24–48 hours.
- Obtain ECG as soon as possible after starting treatment then continue monitoring in those taking medicines that increase plasma-piperaquine concentration, in children who are vomiting, in females, or in the elderly.

Directions for administration: Tablets to be taken at least 3 hours before and at least 3 hours after food. Tablets may be crushed and mixed with water immediately before administration.

Doxycycline

ATC code: J01AA02

Capsule, 100 mg (as HCl), LOU 2

Tablet (dispersible, 100 mg (as monohydrate), LOU 2

Indications and dose

Adult

Supplement to quinine or artesunate treatment for multidrug-resistant Plasmodium falciparum malaria, oral: 100 mg twice daily for 7–10 days

Paediatric

Supplement to quinine or artesunate treatment for multiple-drug-resistant malaria, oral

Child over 8 years: 2 mg/kg (maximum 100 mg) twice daily for 7–10 days

Contraindications: Pregnancy, porphyria, SLE

Precautions: Avoid exposure to sunlight or sunlamps, photosensitivity reported.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Avoid (or use with caution).

Adverse effects: Common: GI disturbances, nausea, vomiting, diarrhoea, anorexia, flushing, tinnitus, photosensitivity. Uncommon: Rash, stomatitis, bone deformity, fungal overgrowth. Rare: Photo-onycholysis, nail discoloration, oesophageal ulcers (due to partly swallowed tablets), *C. difficile* infection, hepatitis, fatty liver degeneration, headache and visual disturbances which may indicate benign intracranial hypertension, hypersensitivity reactions including SJS.

Interactions with other medicines (*indicates serious):

Antacids (aluminium hydroxide, magnesium hydroxide): reduced absorption of doxycycline.

Carbamazepine: accelerated metabolism of doxycycline (reduced effect).

Ciclosporin: possibly increased plasma ciclosporin concentration.

Ferrous salts: absorption of oral ferrous salts reduced by doxycycline, absorption of doxycycline reduced by oral ferrous salts.

Methotrexate: increased risk of methotrexate toxicity.

Phenobarbital: metabolism of doxycycline accelerated (reduced plasma concentration).

Phenytoin: increased metabolism of doxycycline (reduced plasma concentration).

Rifampicin: plasma doxycycline concentration possibly reduced.

* Warfarin: anticoagulant effect possibly enhanced.

Notes:

» Patient advice: Capsules should be swallowed whole with plenty of fluid while sitting or standing to prevent oesophageal irritation. Should be given with food or milk, to counter gastric irritation. For use only in combination with quinine or artesunate.

Primaquine

ATC code: P01BA03

Tablet, 7.5 mg (as diphosphate), LOU 3

Tablet, 15 mg (as diphosphate), LOU 3

Indications and dose

Adult

Only for use to achieve radical cure of P. vivax and P. ovale infections (after standard therapy), oral: 250 micrograms/kg daily (or 15 mg daily) for 14 days, 750 micrograms/kg once a week for 8 weeks,

Gametocytocidal treatment of P. falciparum malaria (after standard blood schizontocide therapy), oral: 250–500 micrograms/kg as a single dose

Paediatric

Radical cure of P. vivax and P. ovale infections after standard artemisinin-based combination therapy, oral

Child: 250 micrograms/kg daily for 14 days

In mild to moderate G6PD deficiency, use 500–750 micrograms/kg once a week for 8 weeks.

Contraindications: Conditions that predispose to granulocytopenia including active rheumatoid arthritis and lupus erythematosus, severe G6PD deficiency.

Precautions: Monitor blood count, if methaemoglobinaemia or haemolysis occur, withdraw treatment and consult physician, mild to moderate G6PD deficiency.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Primaquine is metabolized by the liver, use with caution in patients with liver impairment and monitor liver function tests.

Adverse effects: Common: Anorexia, nausea and vomiting, abdominal pain, dizziness, headache. Infrequent: Acute haemolytic anaemia (frequently in G6PD deficiency). Rare: Hypertension, methaemoglobinaemia, haemoglobinuria, agranulocytosis, granulocytopenia and leukopenia.

Interactions with other medicines (*indicates serious):

» Artemether + lumefantrine: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

Quinine

ATC code: P01BC01

Injection, 300 mg/mL (as HCl) in 2-mL amp, LOU 3

Tablet (f/c), 300 mg (as sulphate or bisulphate), LOU 2

Indications and dose

Adult

Severe malaria (in patients unable to take quinine oral), by slow IV infusion (over 4 hours): Initially 20 mg/kg followed by 10 mg/kg every 8 hours until the patient can take a course of artemether-lumefantrine orally. If AL is not available, treat with oral quinine given at 10 mg/kg every 8 hours to complete a total of 7 days.

Uncomplicated malaria in pregnancy in the first trimester, oral: 10 mg/kg 3 times a day for 7 days (quinine sulphate)

Paediatric

Severe malaria, oral

Child: 20 mg/kg (quinine dihydrochloride) followed by 10 mg/kg (quinine HCl) every 8 hours until the patient can take a complete course of artemether–lumefantrine orally. If AL is not available, treat with oral quinine given at 10 mg/kg every 8 hours to complete a total of 7 days. The initial dose should be halved in patients who received quinine or quinidine during the previous 12–24 hours or mefloquine in the last 7 days.

Contraindications: Haemoglobinuria, optic neuritis, tinnitus, myasthenia gravis.

Precautions: Atrial fibrillation, conduction defects, heart block, monitor for signs of cardiac toxicity and hypoglycaemia during IV use, renal impairment, G6PD deficiency.

Renal impairment: Reduce parenteral maintenance dose for malaria treatment.

Give a lower dose at increased intervals with oral therapy. Mild impairment: administer every 8 hours, moderate impairment: administer every 12 hours, severe impairment: administer every 24 hours.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common: Cinchonism (tinnitus, headache, blurred vision, temporary blindness, altered auditory acuity, nausea, diarrhoea, hot and flushed skin, rashes, confusion), hypersensitivity reactions, GI disturbances, CNS disturbances. Uncommon: Hypoglycaemia, especially after parenteral administration, caused by increased insulin release (also associated with severe malaria and therefore a poor prognostic sign), asthma. Rare: Haemorrhage and renal damage (culminating in acute renal failure and anuria), blood disorders, prolonged QT interval, angioedema.

Interactions with other medicines (*indicates serious):

- *Artemether + lumefantrine: risk of ventricular arrhythmias (manufacturer of artemether with lumefantrine advises to avoid concomitant use).
- Chloroquine: increased risk of ventricular arrhythmias.
- *Digoxin: plasma concentration of digoxin increased.
- *Mefloquine: increased risk of convulsions, but should not prevent the use of IV quinine in severe cases.
- Suxamethonium: possibly enhanced effects of suxamethonium.

Notes:

- Use only in the management of severe malaria. To avoid resistance, quinine should always be used in combination with either doxycycline (not in children under 8 years), clindamycin or sulfadoxine + pyrimethamine (SP) where there is no SP resistance. Clindamycin dose for combination therapy: 7–13 mg/kg (maximum 450 mg) every 8 hours for 7 days.
- Patient advice If all or part of a dose is vomited within 1 hour, the same amount must be re-administered immediately.
- IV administration: give by slow IV infusion over 4 hours.
- Quinine (anhydrous base) 100 mg ≡ quinine bisulphate 169 mg ≡ quinine dihydrochloride 122 mg quinine sulphate 121 mg.
- Very toxic in overdosage, immediate medical attention required.

7.5.3.2. For Prophylaxis

Atovaquone + Proguanil

ATC code: P01BB51

Tablets (f/c), 62.5 mg (HCl) + 25 mg, LOU 4

Tablet (f/c), 250 mg (HCl) + 100 mg, LOU 4

Indications and dose

Adult

Prophylaxis of falciparum malaria, particularly where resistance to other antimalarial drugs suspected, oral, body weight 40 kg and above: 1 tablet once daily, to be started 1–2 days before entering endemic area and continued for 1 week after leaving

Precautions: Diarrhoea or vomiting (reduced absorption of atovaquone) efficacy not evaluated in cerebral or complicated malaria (including hyperparasitaemia, pulmonary oedema or renal failure)

Pregnancy: Manufacturer advises use only if potential benefit outweighs risk.

Breastfeeding: Use only if no suitable alternative available.

Renal impairment: Avoid for malaria prophylaxis (and if possible for malaria treatment) if eGFR less than 30 mL/min/1.73 m2

Adverse effects: Common or very common: Abdominal pain, appetite

Decreased, cough, depression, diarrhoea, dizziness, fever, headache, nausea, skin reactions, sleep disorders, vomiting. Uncommon: Alopecia, anxiety, blood disorder, hyponatraemia, oral disorders, palpitations. Frequency not known: Hallucination, hepatic disorders, photosensitivity reaction, seizure, SJS, tachycardia, vasculitis.

Interactions with other medicines: Rifampicin moderately decreases the exposure to antimalarials (atovaquone)

Notes:

- **Patient and Caregiver advice**: Warn travelers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return.

Doxycycline

ATC code: J01AA02

Capsule, 100 mg (as HCl), LOU 2

Indications and dose

Adult

Short-term prophylaxis of malaria, oral: 100 mg daily for up to 8 weeks, doxycycline should be started on the day before exposure and continued for 4 weeks after last risk of exposure.

Paediatric

Short-term prophylaxis of multiple-drug-resistant P. falciparum malaria, oral

Child over 8 years: 2 mg/kg (maximum 100 mg) daily for up to 8 weeks, doxycycline should be started on the day before exposure and continued for 4 weeks after last risk of exposure.

Contraindications: Pregnancy, porphyria, SLE

Precautions: Avoid exposure to sunlight or sunlamps, photosensitivity reported

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Avoid (or use with caution).

Adverse effects: Common: GI disturbance, nausea, vomiting, diarrhoea, anorexia, flushing, tinnitus, photosensitivity. Uncommon: Rash, stomatitis, bone deformity, fungal overgrowth. Rare: Photo-onycholysis, nail discoloration, oesophageal ulcers (due to partly swallowed tablets), *C. difficile* infection, hepatitis, fatty liver degeneration, headache and visual disturbances which may indicate benign intracranial hypertension, hypersensitivity reactions, including SJS.

Interactions with other medicines (*indicates serious):

- Antacids (aluminium hydroxide, magnesium hydroxide): reduced absorption of doxycycline.
- Carbamazepine: accelerated metabolism of doxycycline (reduced effect).
- *Ciclosporin: possibly increased plasma ciclosporin concentration.
- Ferrous salts: absorption of oral ferrous salts reduced by doxycycline, absorption of doxycycline reduced by oral ferrous salts.
- Methotrexate: increased risk of methotrexate toxicity.
- Phenobarbital: metabolism of doxycycline accelerated (reduced plasma concentration).
- Phenytoin: increased metabolism of doxycycline (reduced plasma concentration).
- Rifampicin: plasma doxycycline concentration possibly reduced.
- *Warfarin: anticoagulant effect possibly enhanced.

Notes:

- Patient advice: Capsules should be swallowed whole with plenty of fluid while sitting or standing to prevent oesophageal irritation. May be given with food or milk, to counter gastric irritation.
- **Special notes:** WHO age/weight restriction: > 8 years.
- Should not be used in children under 8 years: deposition of tetracyclines in growing bones and teeth (by binding to calcium) causes staining and occasionally dental hypoplasia.

Mefloquine

ATC code: P01BC02

Tablet, 250 mg (as HCl), LOU 4

Indications and dose

Adult

Prophylaxis of malaria, oral: 250 mg once a week

Paediatric

Prophylaxis of malaria for travelers to areas with high risk of multiple-drug-resistant P. falciparum, oral

Child over 3 months or 5 kg: 5 mg/kg (maximum 250 mg) once a week; prophylaxis should start 1–3 weeks before departure and continue for 4 weeks after last exposure; round dose to the nearest quarter of a tablet.

Contraindications: History of neuropsychiatric disorders including depression or convulsions, hypersensitivity to quinine.

Precautions: Avoid use in cardiac conduction disorders and in epilepsy. Skilled tasks: Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Renal impairment: Use with caution in severe renal impairment, otherwise dose reduction not needed.

Hepatic impairment: Mefloquine is metabolized by the liver and eliminated by the biliary system. It should be used with caution in patients with disorders of the biliary system who may not be able to clear the drug. Avoid use for prophylaxis in severe liver disease.

Adverse effects: Common: Nausea, vomiting, diarrhoea, abdominal pain, anorexia, headache, dizziness (can be severe), loss of balance, somnolence, insomnia and abnormal dreams. Uncommon: Circulatory disorders, tachycardia, bradycardia, cardiac conduction disorders, muscle weakness, myalgia, arthralgia, rash, urticaria, pruritus, alopecia, disturbances in liver function tests, visual disturbances, tinnitus, vestibular disorders, seizures. Rare and very rare: Neuropsychiatric disorders occur in at least 1:10 000 patients treated with mefloquine and the incidence is thought to be up to 1:1000 when used at treatment doses. These include sensory and motor neuropathies, tremor, ataxia, anxiety, depression, suicidal ideation, confusion, hallucinations, panic attacks, emotional instability, aggression, agitation and psychoses. Hyperpyrexia, leukopenia, leukocytosis, thrombocytopenia, SJS, atrioventricular block and encephalopathy.

Interactions with other medicines (*indicates serious):

*Artemether + lumefantrine: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

Atenolol: increased risk of bradycardia.

*Carbamazepine: antagonism of anticonvulsant effect.

*Chloroquine: increased risk of convulsions.

Digoxin: possibly increased risk of bradycardia.

*Ethosuximide: antagonism of anticonvulsant effect.

Phenytoin: antagonism of anticonvulsant effect.

Propranolol: increased risk of bradycardia.

*Quinidine: increased risk of ventricular arrhythmias.

*Quinine: increased risk of convulsions, but should not prevent the use of IV quinine in severe cases.

*Valproic acid: antagonism of anticonvulsant effect.

Notes:

- Special Notes: WHO age/weight restriction: > 5 kg or > 3 months.

» Patient advice: Warn travelers about the importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of an immediate visit to doctor if ill within 1 year and especially within 3 months of potential exposure.

» Patients should be informed about adverse effects associated with mefloquine and if they occur, advised to seek medical advice on alternative antimalarials.

» Mefloquine tablets may be crushed and mixed with food such as jam or honey just before administration.

» 1 tablet = 228 mg base (250 mg salt).

Proguanil

ATC code: P01BB01

Tablet, 100 mg (as HCl), LOU 2

Indications and dose

Prophylaxis of malaria: Start taking 1–2 days before entering and continue for 4 weeks after leaving an endemic area.

Adult

Prophylaxis of malaria, oral: 200 mg daily, after food

Paediatric

Prophylaxis of malaria, oral

Child under 1 year: 25 mg daily

Child 1–4 years: 50 mg daily

Child 5–8 years: 100 mg daily

Child 9–12 years: 150 mg daily

Renal impairment: Mild: half dose. Moderate: quarter dose every 48 hours. Severe: quarter dose once weekly.

Hepatic impairment: Metabolized by the liver to the active metabolite so unlikely to be effective in patients with severe liver impairment.

Adverse effects: Common: Mild gastric intolerance, diarrhoea, constipation, nausea, vomiting, stomatitis. Infrequent: Mouth ulcers, vertigo, reversible alopecia, skin reactions. Rare: Megaloblastic anaemia and pancytopenia (more likely with renal impairment), cholestasis, vasculitis, hepatitis, seizures, psychosis, hypersensitivity reactions such as urticaria and angioedema.

Interactions with other medicines (*indicates serious):

*Artemether + lumefantrine: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

Pyrimethamine: increased antifolate effect.

Warfarin: isolated reports of enhanced anticoagulant effect.

Notes:

» Patient advice Warn travelers about the importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return.

» Approximately 3% of Caucasians cannot metabolize proguanil to cycloguanil, the active metabolite, and these people are effectively only receiving the chloroquine component of their therapy. These patients also have an increased risk of adverse effects, especially GI Adverse effects.

» Tablets may be crushed and mixed with food such as milk, jam or honey just before administration.

Sulfadoxine + Pyrimethamine

ATC code: P01BD51

Tablet, 500 mg + 25 mg, LOU 2

Indications and dose

Adult

Malaria prophylaxis, oral: Sulfadoxine 1.5 g + pyrimethamine 75 mg (3 tablets) as a single dose

Paediatric

Malaria prophylaxis, oral

Child 5–10 kg: Half a tablet

Child 11–20 kg: 1 tablet as a single dose

Child 21–30 kg: 1½ tablets as a single dose

Child 31–45 kg: 2 tablets as a single dose

Contraindications: Hypersensitivity to sulfonamides or pyrimethamine, severe hepatic or renal impairment (except where no alternative treatment available).

Precautions: Avoid in blood disorders unless under specialist supervision, discontinue immediately if blood disorder occurs, rash, sore throat, mouth ulcers or shortness of breath, G6PD deficiency, predisposition to folate deficiency.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: No information available.

Adverse effects: Common: Rashes, pruritus, slight hair loss, GI disturbances including nausea, vomiting, stomatitis, fatigue, headache, fever, polyneuritis. Rare: Pulmonary infiltrates such as eosinophilic or allergic alveolitis (if symptoms of cough or shortness of breath, withdraw treatment), rarely erythema multiforme (SJS), toxic epidermal necrolysis, hepatitis, leukopenia, thrombocytopenia, megaloblastic anaemia and purpura.

Interactions with other medicines (*indicates serious):

*Artemether + lumefantrine: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

*Ciclosporin: increased risk of nephrotoxicity.

*Folate/folic acid: concurrent use should be avoided as folate may antagonize the effect of sulfadoxine + pyrimethamine.

*Methotrexate: antifolate effect of methotrexate increased, risk of methotrexate toxicity increased.

*Phenytoin: plasma phenytoin concentration possibly increased, increased antifolate effect.

*Sulfadiazine: increased antifolate effect.

*Sulfamethoxazole + trimethoprim: increased antifolate effect.

Thiopental: enhanced effects of thiopental.

*Trimethoprim: increased antifolate effect.

*Warfarin: enhanced anticoagulant effect.

Notes:

» Sulfadoxine + pyrimethamine monotherapy is no longer recommended as this is likely to result in increasing levels of parasite resistance to this drug.

7.5.4. Antipneumocystosis and Antitoxoplasmosis Medicines

Sulfamethoxazole + Trimethoprim (Co-Trimoxazole)

ATC code: J01EE01

Injection, 80 mg + 16 mg/mL in 5-mL amp, 80 mg + 16 mg/mL in 10-mL amp, LOU 4

Oral liquid, 40 mg + 8 mg/mL, LOU 4

Tablet, 800 mg + 160 mg (scored), LOU 4

Indications and dose

Adult

Pneumocystis jiroveci (Pneumocystis carinii) pneumonia, oral or by IV infusion: Sulfamethoxazole 25 mg/kg three times daily + trimethoprim5 mg/kg three times daily for 21 days

Prophylaxis of P. jiroveci pneumonia, oral: Sulfamethoxazole 800 mg + trimethoprim 160 mg once daily

Paediatric

Doses are expressed in terms of the trimethoprim component.

P. jiroveci (P. carinii) infections, oral or IV

Infant or child over 1 month: 10 mg/kg every 12 hours for 14–21 days; total daily dose may alternatively be given in 3–4 divided doses; IV route is preferred

Prophylaxis for P. jiroveci (P. carinii) infections, oral

Infant or child under 6 months: 20 mg once daily

Child 6 months–5 years: 40 mg once daily

Child 6–12 years: 80 mg once daily

Contraindications: Hypersensitivity to sulfonamides or trimethoprim, porphyria, megaloblastic anaemia, severe renal impairment, severe hepatic impairment.

Precautions: Mild to moderate renal impairment, maintain adequate fluid intake (to avoid crystalluria), avoid in blood disorders (unless under specialist supervision), monitor blood counts on prolonged treatment, discontinue immediately if blood disorder develops, rash (discontinue immediately), predisposition to folate deficiency, asthma, G6PD deficiency, jaundiced neonates.

Renal impairment: Severe impairment: avoid use. Moderate impairment: use half normal dose. Plasma monitoring may be required with high doses in renal impairment, seek expert advice.

Hepatic impairment: Severe impairment: avoid use.

Adverse effects: Some adverse effects may be hypersensitivity reactions (see below

Incidence of some adverse effects (rash, fever, nausea, neutropenia, thrombocytopenia, raised hepatic aminotransferases) is substantially higher in patients with AIDS. Common: Fever, nausea, vomiting, diarrhoea, anorexia, rash, itch, stomatitis, hyperkalaemia, thrombocytopenia, photosensitivity. Headache, drowsiness, blood disorders (including neutropenia, leukopenia, thrombocytopenia, eosinophilia, megaloblastic anaemia, methaemoglobinaemia). Rare: Erythema, vasculitis, hyponatraemia, hypoglycaemia, pancreatitis, hepatitis, jaundice, hepatic necrosis, crystalluria, urinary obstruction with anuria/oliguria, lowered mental acuity, depression, tremor, ataxia (after IV use in HIV patients), antibiotic-associated colitis, CDAD, aseptic meningitis. Hypersensitivity: May present with fever, dyspnoea, cough, rash, eosinophilia, the most serious effects include anaphylaxis, SJS, toxic epidermal necrolysis, serum sickness-like syndrome, lupus-like syndrome, pneumonitis, hepatitis, interstitial nephritis, systemic vasculitis and pancytopenia.

Interactions with other medicines (*indicates serious):

Trimethoprim is a folate antagonist and will add to the effects on bone marrow of other folate antagonists, e.g., pyrimethamine.

Trimethoprim can cause hyperkalaemia, administration with potassium supplements or other drugs which also cause potassium retention can further increase potassium concentration.

Trimethoprim with sulfamethoxazole can cause nephrotoxicity, giving with other nephrotoxic drugs may cause additional renal adverse effects.

*Azathioprine: increased risk of haematological toxicity.

*Ciclosporin: increased risk of nephrotoxicity, plasma ciclosporin concentration possibly reduced by IV trimethoprim.

*Dapsone: plasma concentration of both dapsone and trimethoprim may increase with concomitant use.

Digoxin: plasma concentration of digoxin possibly increased.

Lamivudine: plasma concentration of lamivudine increased (avoid concomitant use of high-dose sulfamethoxazole + trimethoprim).

*Mercaptopurine: increased risk of haematological toxicity.

*Methotrexate: antifolate effect of methotrexate increased (avoid concomitant use), risk of methotrexate toxicity increased.

*Phenytoin: antifolate effect and plasma phenytoin concentration increased.

Procainamide: increased plasma procainamide concentration.

*Pyrimethamine: increased antifolate effect.

*Sulfadoxine + pyrimethamine: increased antifolate effect.

Thiopental: enhanced effects of thiopental.

*Warfarin: enhanced anticoagulant effect.

Notes:

- Oral dose is best given with or after food.
- Attention should be paid to the folate status of the patient should treatment be prolonged or high dose.
- Local antimicrobial patterns need to be considered.
- **Dilution and administration:**

  For intermittent IV infusion may be further diluted in glucose 5% and 10% or sodium chloride 0.9% or Ringer's IV solution. Must be further diluted, dilute each 5 mL of injection solution to 125 mL. Infuse over 60–90 minutes (but may be adjusted according to fluid requirements). If fluid restriction necessary, 5 mL may be diluted with 75 mL of glucose 5% and the required dose infused over a maximum of 60 minutes. Check container for haze or precipitant during administration. In severe fluid restriction may be given undiluted via a central venous line.

Pyrimethamine

ATC code: P01BD01

Tablet, 25 mg, LOU 4

Indications and dose

Adult

Prevention of congenital transmission of toxoplasmosis (in second and third trimesters of pregnancy), oral: 25 mg daily for 3–4 weeks

Toxoplasmosis in immunodeficiency, oral: 200 mg in divided doses on first day, then 75–100 mg daily for at least 6 weeks, followed by a suppressive dose of 25–50 mg daily

Chorioretinitis, oral: 75 mg daily for 3 days, then 25 mg daily for 4 weeks, in unresponsive patients, 50 mg daily for a further 4 weeks

Paediatric

Note: Calcium folinate must always be administered with pyrimethamine to prevent haematological toxicity. Because of the long half-life of pyrimethamine, calcium folinate administration should be continued for 1 week after pyrimethamine has been discontinued.

Congenital toxoplasmosis (in combination with sulfadiazine and calcium folinate), oral

Neonate: 1 mg/kg twice daily for 2 days, then 1 mg/kg once daily for 6 months, then 1 mg/kg three times weekly for a further 6 months. Duration of treatment depends on whether the neonate has overt disease. If without overt disease but born to mother infected during pregnancy, treat for 4 weeks, followed by further courses if infection confirmed.

Toxoplasmosis (in combination with sulfadiazine and calcium folinate), oral

Child over 1 month: 1 mg/kg (maximum 25 mg/dose) twice daily for 3 days, then 1 mg/kg (maximum 25 mg) once daily for at least 6 weeks

Primary prophylaxis of toxoplasmosis (in combination with dapsone [not on EMLc for this indication] and calcium folinate), oral

Child over 1 month: 1 mg/kg once daily; maximum 25 mg daily

Secondary prophylaxis of toxoplasmosis in addition to prophylaxis of Pneumocystis jiroveci (Pneumocystis carinii) pneumonia (in combination with sulfadiazine and calcium folinate), oral

Infant or child: 1 mg/kg once daily; maximum 50 mg daily **Note**: Clindamycin (not on the EMLc for this indication) may be used instead of sulfadiazine in patients intolerant of sulfonamides.

Contraindications: Megaloblastic anaemia.

Precautions: Folate deficiency, blood counts required with prolonged treatment, supplement folate throughout treatment to prevent haematological toxicity, history of seizures (avoid large loading doses), renal impairment, hepatic impairment.

Renal impairment: Use with caution. Dosage adjustment not considered to be necessary in renal impairment.

Hepatic impairment: Use with caution in patients with hepatic impairment.

Adverse effects: Depression of haematopoiesis (with high doses), megaloblastic anaemia, rashes, insomnia, GI disturbances.

Interactions with other medicines (*indicates serious):

*Artemether + lumefantrine: manufacturer of artemether with lumefantrine advises avoid concomitant use.

*Methotrexate: antifolate effect of methotrexate increased.

*Phenytoin: antagonism of anticonvulsant effect, increased antifolate effect.

Proguanil: increased antifolate effect.

*Silver sulfadiazine: increased antifolate effect.

Sulfadiazine: increased antifolate effect.

*Sulfamethoxazole + trimethoprim: increased antifolate effect.

*Trimethoprim: increased antifolate effect.

Zidovudine: increased antifolate effect.

Notes:

- Pyrimethamine-associated reversible bone marrow suppression warrants that a CBC be performed at least weekly while the patient is on daily pyrimethamine and at least monthly while on less than daily dosing. It is also important that calcium folinate be always administered with pyrimethamine and increased doses of calcium folinate may be necessary if marrow suppression occurs.
- Administer pyrimethamine with food to minimize vomiting.
- For the treatment of toxoplasmosis, pyrimethamine must always be taken with

sulfadiazine. Local antimicrobial sensitivity patterns need to be considered. Expert advice essential.

Sulfadiazine

ATC code: J01EC02

Tablet, 500 mg, LOU 4

Indications and dose

Adult

Toxoplasmosis in combination with pyrimethamine, prophylaxis of Pneumocystis jiroveci (Pneumocystis carinii) pneumonia in combination with pyrimethamine, oral: 1 g daily

Paediatric

Congenital toxoplasmosis (in combination with pyrimethamine and calcium folinate), oral

Neonate: 50 mg/kg twice daily for 12 months

Toxoplasmosis (in combination with pyrimethamine and calcium folinate), oral

Child all ages: 25–50 mg/kg (maximum 1–1.5 g per dose) four times daily, followed by secondary prophylaxis therapy

Secondary prophylaxis of toxoplasmosis in addition to prophylaxis of Pneumocystis jiroveci (Pneumocystis carinii) pneumonia (in combination with pyrimethamine and calcium folinate), oral

Child all ages: 85–120 mg/kg daily in 2–4 divided doses

Note: Clindamycin (not on the EMLc for this indication) may be used instead of sulfadiazine in patients intolerant of sulfonamides.
Contraindications: Hypersensitivity to any sulfa drug, porphyria.

Precautions: Renal impairment, hepatic impairment, G6PD deficiency, urinary obstruction, blood dyscrasia.

Hepatic impairment: Use with caution.

Renal impairment: Use with caution in renal impairment. Severe renal impairment: avoid, high risk of crystalluria.

Adverse effects: Common: Nausea. Uncommon: Vomiting, rash, abdominal pain. Rare: Hepatitis, pancreatitis, SJS, crystalluria, blood dyscrasias.

Interactions with other medicines (*indicates serious):
*Ciclosporin: plasma ciclosporin concentration possibly reduced, increased risk of nephrotoxicity.

Methotrexate: risk of methotrexate toxicity increased.

Phenytoin: plasma phenytoin concentration possibly increased.

*Pyrimethamine: increased antifolate effect.

*Sulfadoxine + pyrimethamine: increased antifolate effect.

Thiopental: enhanced effects of thiopental.

*Warfarin: enhanced anticoagulant effect.

Note: Local antimicrobial sensitivity patterns need to be considered.

7.5.5. Antitrypanosomal Medicines

7.5.5.1. Human African Trypanosomiasis

a. **Medicines for the treatment of 1st stage African trypanosomiasis**

Pentamidine Isethionate

ATC code: P01CX01

Powder for injection, 200 mg in vial, LOU 4

Indications

Adult

Haemolymphatic first-stage of rhodesiense and gambiense HAT, by IM injection: 4 mg/kg daily for 7 days or on alternate days for a total of 7–10 doses

Meningoencephalitic stage of T. brucei gambiense (prior to melarsoprol), by IM injection: 4 mg/kg daily on days one and two

Paediatric

Treatment of first-stage trypanosomiasis, by IM

Infant or child: 4 mg/kg daily for 7 days

Contraindications: severe renal impairment, *T. brucei rhodesiense* infection (since primary resistance has been observed).

Precautions: Cerebrospinal fluid examination before treatment (pentamidine not likely to be effective if leukocyte count greater than 5–10 cells/mm3, or trypanosomes detected in cerebrospinal fluid), risk of severe hypotension following administration, hypotension or hypertension, hepatic impairment, hypoglycaemia or hyperglycaemia, leukopenia, thrombocytopenia, anaemia, immunodeficiency (if acute deterioration in bone marrow, renal or pancreatic function, interrupt or discontinue treatment), renal impairment.

Renal impairment: Severe impairment: reduce dose interval (e.g., every alternate day).

Hepatic impairment: Use with caution.

Adverse effects: Common: Pain at injection site. Rare: Diarrhoea, nausea, nephrotoxicity, acute hypotension, hypoglycaemia (may be followed by hyperglycaemia and type I diabetes mellitus), pancreatitis, also hypocalcaemia, GI disturbances, confusion, hallucinations, arrhythmias, thrombocytopenia, leukopenia, abnormal liver function tests, anaemia, hyperkalaemia, rash, SJS, pain, local induration, sterile abscess and muscle necrosis at injection site.

Interactions with other medicines (*indicates serious):

Amphotericin B: possibly increased risk of nephrotoxicity.

Artemether: increased level and toxicity of pentamidine. Avoid concomitant use.

Quinine: increased level and toxicity of pentamidine and quinine. Avoid concomitant use.

Typhoid vaccine: pentamidine may decrease the effect of typhoid vaccine.

Notes:

- A cerebrospinal fluid examination before treatment is required as pentamidine is not effective if trypanosomes are detected in the cerebrospinal fluid or the leukocyte count is above 5–10 cells/mm3.
- Before administration, establish baseline blood pressure and administer with patient lying down, they should remain lying for 1–2 hours after administration.
- Monitor blood pressure and cardiac rhythm during administration and treatment period.
- Hypoglycaemia post-administration is easily prevented by administering oral sugar, in tea or similar, half an hour before administration.
- Periodic ECG is desirable.
- Extreme care should be taken to ensure aseptic technique when administering to avoid the risk of abscess or necrosis at the injection site.
- Reconstitution and administration Reconstitute vial with water for injection to a final concentration of 100 mg/mL. Administer by deep IM injection and preferably into the buttock. Pentamidine isetionate is toxic, care is required to protect personnel during handling and administration.
- **RECONSTITUTION AND ADMINISTRATION:** According to manufacturer's directions.
- Pentamidine is toxic, care is required in order to protect personnel during handling and administration.

Suramin Sodium

ATC code: P01CX02

Powder for injection, 1 g in vial, LOU 4

Indications and dose

Adult

Initial phase of Trypanosoma brucei rhodesiense infection, by slow IV injection: 5 mg/kg on day 1, then 20 mg/kg on days 5, 11, 17, 23, and 30.5 mg/kg on day 31, OR 20 mg/kg every week for five weeks. Maximum dose per injection is 1 g.

Paediatric

Initial phase of Trypanosoma brucei rhodesiense infection, slow IV injection

Child all ages: 5 mg/kg on day 1 (as a test dose) followed by 20 mg/kg on day 3, 10, 17, 24, and 31.

First (test) dose: Administer first dose with particular caution, wait at least 1 minute after injecting the first few microlitres, inject next 0.5 mL over 30 seconds and wait 1 minute, inject the remainder over several minutes.

Contraindications: Previous anaphylaxis or suramin sensitivity, severe liver impairment, severe renal impairment.

Precautions: Debilitated or malnourished patients, albuminuria, onchocerciasis.

Renal impairment: Mild to moderate impairment: use with caution. Severe impairment: avoid use. Suramin is excreted renally at a slow rate due to extensive protein binding. Drug can be excreted in the urine unchanged for 3 months following doses of suramin.

Hepatic impairment: Severe impairment: avoid use. Administration of suramin in individuals with significant hepatic dysfunction, in whom serum albumin levels may be reduced, may result in toxic serum suramin levels due to an increased free fraction of the drug in the plasma.

Adverse effects: Common: Fever, rash, vomiting, nausea and metallic taste, thrombocytopenia, peripheral neuropathy, transient hyperbilirubinaemia, mild proteinuria. Rare: Immediate and potentially fatal allergic reaction with nausea, vomiting, shock and loss of consciousness during first dose (see First (test) dose), albuminuria, abdominal pain, severe diarrhoea, stomal ulceration, exfoliative dermatitis, tiredness, anorexia, malaise, polyuria, thirst, raised liver enzyme values, paraesthesia and hyperaesthesia of palms and soles.

Interactions with other medicines (*indicates serious): There are no known interactions where it is recommended to avoid concurrent use.

Notes:

- Suramin is only effective in the early stages of the illness, in which no CNS involvement has occurred. Suramin crosses the blood-brain barrier poorly, and in later stages where the organism has penetrated the CNS, other agents must be used.
- Cerebrospinal fluid examination should be conducted before treatment.
- Administer only under close medical supervision in hospital and with general condition improved as far as possible before treatments.
- Poor nutritional status increases frequency of adverse reactions, so correct with a protein-rich diet and maintain satisfactory food and fluid intake during treatment.
- Conduct urine tests before treatment and weekly during treatment, reduce dose if moderate albuminuria, discontinue immediately if severe albuminuria or casts in urine.
- Reconstitution of injection Reconstitute in water for injections to produce a final concentration of 10%. The compound deteriorates quickly in air and so should be injected immediately after preparation.

b. Medicines for the treatment of 2nd stage African trypanosomiasis

Eflornithine

ATC code: P01CX03

Injection, 200 mg (as HCl)/mL in 100-mL bottle, LOU 4.

Indications and dose

Adult

Meningoencephalitic stages of *T. brucei gambiense* infection in combination with nifurtimox, *by IV infusion:* 100 mg/kg over 45 minutes every 6 hours for 14 days

Paediatric

Second-stage Trypanosoma brucei gambiense infection, slow IV infusion

Child under 35 kg: 150 mg/kg over 2 hours every 6 hours for 14 days, over 35 kg 100 mg/kg over 2 hours every 6 hours for 14 days

Contraindications: Ineffective in the treatment of Trypanosoma brucei rhodesiense.

Precautions: Hospitalization and close supervision throughout treatment, renal impairment, monitor complete blood and platelet counts for bone marrow suppression (severe anaemia, leukopenia or thrombocytopenia requires an interruption in treatment until there is evidence of bone marrow recovery), concurrent bacterial infections.

Renal impairment: Dosage adjustment may be required in all degrees of renal impairment. Eflornithine is 80% renally excreted.

Interactions with other medicines: There are no known interactions where it is recommended to avoid concurrent use.

Notes:

- Eflornithine HCl concentrate for injection is hypertonic and must be diluted with sterile water for injection before infusion.
- After dilution with sterile water for injection, eflornithine must be used within 24 hours. Bags containing diluted eflornithine should be stored at 4 °C (39 °F) to minimize the risk of microbial proliferation.
- Strict aseptic technique should be used when administering, with frequent replacement of IV cannulas (at least every 2 days).
- Monitoring should continue for up to 4 weeks after finishing treatment.
- Eflornithine in combination with nifurtimox has been recently introduced to reduce duration and workload of eflornithine monotherapy and may delay the appearance of drug resistance. Currently, there is a multicentre trial being conducted which includes assessing the safety and efficacy in children at the same dose as adults.
- DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Melarsoprol (Mel B or Melarsen Oxide- Bal)

ATC code: P01CD01

Injection, 36 mg/mL (3.6%) solution, 5-mL amp (180 mg of active compound), LOU 4.

Indications and dose

Adult

T. brucei rhodesiense and T. brucei gambiense with meningo-encephalitic involvement, slow IV injection: 2.2 mg/kg per day (maximum: 5 mL) once daily for 10 days

Paediatric

T. brucei rhodesiense and T. brucei gambiense with meningo-encephalitic involvement, slow IV injection, slow IV injections

Child: 2.2 mg/kg per day (maximum: 5 mL) once daily for 10 days

Contraindications: Ingestion of alcohol during treatment.

Precautions: Hospitalization and close medical supervision required throughout treatment, reactive encephalopathy (immediate treatment suspension essential), treat intercurrent infections such as pneumonia and malaria before melarsoprol administration, malnutrition (if possible, correct with protein-rich diet), G6PD deficiency, leprosy (may precipitate erythema nodosum), fever, avoid use during influenza epidemics (increased risk of reactive encephalopathy in febrile patients), avoid extravasation.

Adverse effects: Common: Fatal reactive, peripheral neuropathy, Jarisch-Herxheimer reaction (fever and chills may also occur, resulting from trypanosome destruction), headache, diarrhoea, vomiting, arthralgia, fever, skin reactions, thrombophlebitis. Frequency unknown: Reactive encephalopathy appears to be more frequent in children. Myocardial damage, albuminuria, hypertension, hyperthermia, urticaria. Rare: Agranulocytosis, aplastic anaemia, thrombocytopenia, hypersensitivity reactions (especially on second or subsequent doses), haemorrhagic encephalopathy, exfoliative dermatitis.

Fatal reactive encephalopathy, also known as "arsenical encephalopathy", is characterized by fever, headache, tremor, slurred speech, seizures and ultimately coma (occurs in 3–10% of patients treated with melarsoprol, and is fatal in approximately 50% of those who experience it).

Interactions with other medicines: Alcohol: combination contraindicated as increases toxicity of melarsoprol.

Notes:

- Melarsoprol is very toxic with a 3–10% lethality. It should therefore be used only for the approved indications where close observation can be maintained and it can be administered by experienced personnel. Melarsoprol is strictly for IV use only.
- Relapse has been reported in up to 20–30% of late-stage trypanosomiasis patients after treatment with melarsoprol. This appears related to resistance, although reinfection or inadequate CSF concentrations of the drug may be responsible in some cases. Re-treatment with melarsoprol in these patients has not been consistently effective and is not recommended. Eflornithine therapy should be considered.
- Patients should remain supine and fasting for at least 2 hours after injection to reduce GI adverse effects.
- **Administration:** Melarsoprol should be administered by slow IV injection as a

3.6% solution in propylene glycol. Because melarsoprol injection is intensely irritating due to its propylene glycol content, care should be taken to avoid leakage into the surrounding tissues.

» Extravasation during IV administration may result in extreme local tissue damage and destruction.

» Prednisolone 1 mg/kg once daily should be administered concurrently to all patients for the duration of melarsoprol therapy.

Nifurtimox

ATC code: P01CC01

Tablet, 120 mg, LOU 4

Indications and dose

Adult

Acute American trypanosomiasis (Chagas disease), oral: 8–10 mg/kg daily in three divided doses for 90 days

Paediatric

Acute phase or early chronic phase of Chagas disease (American trypanosomiasis), oral **Neonate, infant, or child under 40 kg:** 15–20 mg/kg daily in three divided doses for 60 days

Child 40 kg or over: 12.5–15 mg/kg daily in three divided doses for 60 days; administer every 8 hours after meals

Chronic phase of Chagas disease (American trypanosomiasis), oral

Infant or child: 8–10 mg/kg daily in three divided doses for 60 days; administer every 8 hours after meals

Contraindications: Pregnancy, porphyria, hypersensitivity to hydantoin, allergic afflictions (particularly those involving skin manifestations).

Precautions: Close medical supervision required in patients with history of cerebral damage or predisposition to seizures, psychosis or serious behavioural alterations, co-administer aluminium hydroxide to reduce GI irritation, renal impairment, hepatic impairment.

Renal impairment:

» Mild and moderate impairment: dosage adjustment may be required due to increased serum levels and toxicity of nifurtimox.

» Severe impairment/failure: avoid use (limited data available).

Hepatic impairment: Hepatic function impairment may increase blood concentrations of this medication, increasing the risk of adverse effects.

Adverse effects: Common: Rash, anorexia, loss of weight, nausea, vomiting, gastric pain, headache, vertigo. Uncommon: Memory loss, sleep disturbances, excitability, myalgia, arthralgia, peripheral neuritis (may require discontinuation). Rare: Tremors, seizures, psychotic reactions, suicidality.

Interactions with other medicines: There are no known interactions where it is recommended to avoid concomitant use.

Notes:

» Nifurtimox is best taken with or after meals to minimize GI irritation, every 8 hours.

» Tablets should be taken three times daily, preferably in the morning, at noon and at night, after meals.

» Infants may take it crushed and mixed with a small amount of food. In this case it is convenient to give the medication before the full meal.

7.6. Medicines For Ectoparasitic Infections

Ivermectin

ATC code: P02CF01

Tablet (scored), 3 mg, LOU 3

Indications and dose

Adult

Chronic strongyloides infection, oral: 200 micrograms/kg daily for 2 days

Onchocerciasis, oral: 150 micrograms/kg for 1 dose; retreatment at intervals of 6 to 12 months, depending on symptoms; must be given until adult worms die

Paediatric

Chronic strongyloides infection, oral

Child over 5 years: 200 micrograms/kg daily for 2 days

Adverse effects: Common or very common Skin reactions

Interactions: Ivermectin potentially increases the anticoagulant effect of coumarins.

Note:

» The treating physician should determine the age limits and clinical suitability of this specific therapy.

8. Antimigraine Medicines

8.1. Treatment of Acute Migraine Attack

For treatment of an acute attack, early use of simple analgesics is often effective.

Acetylsalicylic Acid (Aspirin) (Aspirin)

ATC code: B01AC06

Tablet, 300 mg, LOU 2

Indications and dose

Adult

Acute migraine attack, oral: 300 mg at first sign of attack, repeated every 4to 6 hours if necessary, maximum, 4 g daily

Paediatric: Child under 16 years: Not recommended

Contraindications, precautions, use in hepatic and renal impairment, pregnancy and breastfeeding, adverse effects, interactions with other medicines and notes:

See Acetylsalicylic acid (Aspirin) under section 3.1 Non-Opioids and Non Steroidal Anti-inflammatory Medicines

Ibuprofen

ATC code: M01AE01

Tablet, 200 mg, LOU 2

Indications and dose

Adult

Acute migraine, oral: 400 to 600 mg for 1 dose, to be taken as soon as migraine symptoms develop, increase if necessary up to 600 mg 4 times a day

Paediatric

Acute migraine attack, oral

Infant or **child over 3 months**: 5 to 10 mg/kg three or four times daily, maximum dose is 40 mg/kg/day

Contraindications, precautions, use in hepatic and renal impairment, pregnancy and breastfeeding, adverse effects, interactions with other medicines and notes:

See Ibuprofen under section 3.1 Non-Opioids and Non Steroidal Anti-inflammatory Medicines

Paracetamol (Acetaminophen)

ATC code: N02BE01

Oral liquid, 120 mg/5 mL, LOU 1

Tablet, 500 mg, LOU 1

Indications and dose

Adult

Acute migraine attack, oral: 0.5 to 1 g at first sign of attack, repeated every 4 to 6 hours if necessary, maximum, 4 g daily

Paediatric

Acute migraine attack, oral

Infant or **child:** 15 mg/kg, up to 1 g, every 4 to 6 hours as necessary, maximum 60 mg/kg in 24 hours

Contraindications, precautions, use in hepatic and renal impairment, pregnancy and breastfeeding, adverse effects, interactions with other medicines and notes:

See Paracetamol under section 3.1 Non-Opioids and Non Steroidal Anti-inflammatory Medicines

Sumatriptan

ATC Code: N02CC01

Tablet, 25mg, 50mg LoU 5

Indications and dose for oral preparation

For acute management of migraines headaches with or without aura.

Adult

Administer 25-100mg/ day as a single dose; if response to the first dose is observed a second dose can be administered. Separate doses by at least 2 hours.

Doses of 50 mg and 100 mg may provide a greater effect than the 25-mg dose

The recommended maximum dose is 200 mg/day

Elderly:

Use not recommended due to higher incidence of adverse effects

Paediatric

Safety and efficacy is not established for patients <18 years

Dosage Modifications

Renal impairment

There is inconclusive data on safety profile in renal insufficiency.

Hepatic impairment:

Maximum single dose should not exceed 50 mg in patients with mild to moderate hepatic impairment.

It is contraindicated in severe hepatic impairment.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients, Concurrent or recent (past 2 weeks) use of monoamine oxidase-A Inhibitor, Ischemic coronary artery disease (CAD) (angina pectoris, history of myocardial infarction, or documented silent ischemia) or coronary artery vasospasm, Prinzmetal's angina, Wolff-Parkinson, History of stroke, transient ischemic attack, or hemiplegic or basilar migraine, Peripheral vascular disease, Ischemic bowel disease, Uncontrolled hypertension, Recent (within 24 hours) use of another 5-HT1 agonist (e.g., another triptan) or of an ergotamine-containing medication.

Precautions:

Arrhythmias, Chest/throat/neck/jaw pain, tightness, pressure, or heaviness, evaluate for coronary artery disease in patients at high risk, Cerebral hemorrhage, subarachnoid hemorrhage, stroke, Medication overuse headache where detoxification may be necessary, Serotonin syndrome, Seizures.

Pregnancy:

Use with caution. Based on animal data, may cause fetal harm associated with embryolethality, fetal abnormalities, and pup mortality. Studies have also suggested an increased risk of pre-eclampsia.

Lactation:

There is inconclusive data on lactation.

Adverse effects:

Higher doses may have a greater risk of adverse reactions with the most common being, paresthesia, warm/cold sensation, chest pain/tightness/pressure and/or heaviness, neck/throat/jaw pain/tightness/pressure, other sensations of pain/pressure/tightness/heaviness, vertigo, and malaise/fatigue.

Interactions with other medicines (*indicates serious): Ergot-Containing Drugs, Monoamine Oxidase-A Inhibitors, *Other 5-HT1 Agonists (e.g *amlotriptan, *zolmitriptan, *rizatriptan - administration within 24 hours of each other is contraindicated), Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors (Serotonin Syndrome may occur).

Notes:

- Use only if a clear diagnosis of migraine headache has been established.
- It is not indicated for the prophylactic therapy of migraine attacks.
- It is not indicated for the treatment of cluster headache.

8.2. Prophylaxis of Migraine

Propranolol

ATC code: C07AA05

Tablet, 40 mg (as HCl), LOU 4

Indications and dose

Adult

Prophylaxis of migraine, oral: Initially 40 mg 2–3 times daily, increased by same amount at weekly intervals if necessary, usual maintenance dose is in the range 80–160 mg daily 20 mg 2–3 times daily

Paediatric

Migraine prophylaxis, oral

Child over 2 years: 200–500 micrograms/kg three times daily, maximum 4 mg/kg daily; usual dose 10–20 mg 2–3 times daily

Contraindications: Asthma, history of bronchospasm, uncontrolled heart failure, marked bradycardia, hypotension, sick sinus syndrome, second or third-degree atrioventricular block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease, phaeochromocytoma.

Precautions: Avoid abrupt withdrawal, first-degree atrioventricular block, portal hypertension, diabetes mellitus, history of obstructive airways disease, renal impairment, liver disease, myasthenia gravis, history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline)).

Renal impairment: Severe: start with small dose, higher plasma concentrations after oral administration, may reduce renal blood flow and adversely affect renal function.

Hepatic impairment: Reduce oral dose.

Adverse effects: Nausea, diarrhoea, fatigue, insomnia, nightmares, dyspnoea, bronchospasm, peripheral vasoconstriction, exacerbation of Raynaud syndrome, bradycardia, heart failure, hypotension, conduction disorders. Rash, exacerbation of psoriasis, muscle cramp, dry eyes. Hypersensitivity reaction, thrombocytopenic purpura, liver function abnormality, alopecia, cardiac arrest.

Interactions with other medicines (*indicates serious):

*Bupivacaine, *chlorpromazine, oral contraceptives, dexamethasone, diazepam, digoxin, enalapril, *epinephrine, furosemide, halothane, hydrochlorothiazide, hydrocortisone, ibuprofen, insulins, ketamine, *lidocaine, mefloquine, neostigmine, *nifedipine, nitrous oxide, prednisolone, *procainamide, pyridostigmine, *quinidine, rifampicin, sodium nitroprusside, spironolactone, suxamethonium, thiopental, vecuronium, *verapamil.

Notes:

- Advise patient or Caregiver not to discontinue abruptly. Given with food.

Topiramate

ATC Code: N03AX11

Tablet, 25mg, 50mg, LoU 5

Indications and dose

For the management and prophylaxis of migraine.

Adult

For patients 12 years of age and older for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. The recommended titration rate for migraine prophylaxis is as follows:

Migraine Prophylaxis Titration Schedule for Patients 12 Years of Age and Older		
Week 1	None	25mg
Week 2	25mg	25mg
Week 3	25mg	50mg
Week 4	50mg	50mg
Dose and titration rate should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.		

Elderly:

Use not recommended due to higher incidence of adverse effects

Paediatric

<12 years: Safety and efficacy not established

Child 12-17 years: 50 to 200 mg/day, or 2 to 3 mg/kg/day. See table above for titration

Dosage Modifications

Renal impairment:

For patients with creatinine clearance <70 mL/min: Reduce dose by 50%

It is cleared by hemodialysis at rate 4-6 times greater than normal; prolonged period of dialysis may decrease topiramate serum concentrations. A supplemental dose may be required.

Hepatic impairment:

Do therapeutic drug monitoring due to decreased clearance of Topiramate.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients,

For the extended release: Within 6 hrs of alcohol intake; patients with metabolic acidosis that are taking metformin concomitantly.

Precautions:

Hyperammonemia and Encephalopathy, Kidney Stones, hypothermia with Concomitant Valproic Acid, acute Myopia and Secondary Angle Closure Glaucoma, Visual Field Defects, Oligohidrosis and Hyperthermia, Metabolic Acidosis, Suicidal Behavior and Ideation, Cognitive/Neuropsychiatric Adverse Reactions, Kidney Stones

Pregnancy:

It can cause fetal harm in pregnancy. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts) and for being small for gestational age.

Lactation:

There is inconclusive data on lactation.

Adverse effects:

Decrease in serum bicarbonate, Anorexia, Confusion, Decreased memory, Nausea, Speech disorder, Abdominal pain, Weight loss, Diplopia, Dizziness, Fatigue, Ataxia, Nervousness,

Paresthesia, Psychomotor slowing, Abnormal vision, Mood problems, Pharyngitis, Tremor, Abnormal gait, Apathy, Asthenia, Dry mouth, Menorrhagia, Skin disorder, Taste change, Edema, Hypertension, Syncope, Bradycardia, Pallor.

Interactions with other medicines (*indicates serious):

Phenytoin, carbamazepine, zonisamide, acetazolamide, pioglitazone, Lithium, Amitriptyline,

*dihydroergotamine, *dihydroergotamine, *dronedarone, *ergotamine,*erythromycin stearate, *ethinylestradiol, *metoclopramide,*norethindrone, *norethindrone acetate, *norethindrone transdermal, *simvastatin, artemether/lumefantrine

Notes:

» Also indicated for Adjunctive Therapy Epilepsy and Monotherapy Epilepsy.

9. Immunomodulators & Antineoplastics

9.1. Immunomodulators For Non-Malignant Disease & Supportive Medicines

Antithymocyte globulin (ATG) (Equine)

ATC code: L04AA03

Injection, 50mg/mL (5-mL vial), LOU 6

Indications and dose

Adult

Treatment of moderate to severe aplastic anaemia as part of standard immunosuppressive therapy in patients who are unsuitable for hematopoietic stem cell transplantation Intravenous infusion: 10-20 mg/kg once daily for 8-14 days, then every other day when needed for a total of 21 doses in 28 days.

Renal allograft as part of standard immunosuppressive therapy

» *Delaying onset of rejection, (start within 24hrs of transplant)*

*Intravenous infusion:*15 mg/kg once daily for 14 days, then every other day when needed for 14 days (total of 21 doses in 28 days).

» *Treatment of rejection*

intravenous infusion: 10-20 mg/kg once daily for 8-14 days, then every other day when needed (total of 21 doses in 28 days).

Paediatric

Moderate to severe aplastic anaemia as part of standard immunosuppressive therapy in patients who are unsuitable for hematopoietic stem cell transplantation.

Intravenous infusion: 10-20 mg/kg once daily for 8-14 days, then every other day when needed for a total of 21 doses in 28 days.

Renal allograft as part of standard immunosuppressive therapy

» *Delaying onset of rejection, (start within 24 hrs of transplant);*

Intravenous infusion: 15 mg/kg once daily for 14 days, then every other day when needed for 14 days (total of 21 doses in 28 days).

» *Treatment of rejection;*

Intravenous infusion: 10-15 mg/kg once daily for 14 days, then every other day when needed (total of 21 doses in 28 days).

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Precautions:

» There is a potential risk of cytokine release syndrome and discontinuation of treatment should be considered.

» Anaphylaxis, including respiratory distress can occur and treatment should be discontinued if anaphylaxis occurs. It is strongly recommended to perform skin testing before commencing treatment to identify those at greatest risk of systemic anaphylaxis. (See notes).

» There is risk of severe and unremitting thrombocytopenia or neutropenia, and discontinuation of treatment should be considered.

Hepatic impairment: No dose adjustments - use with caution.

Renal impairment: No dose adjustments– use with caution.

Pregnancy: Avoid use in pregnancy. Women of childbearing potential should use effective contraception during and up to 10 weeks after completion of therapy.

Breastfeeding: Not recommended for use during breastfeeding.

Adverse effects: Sepsis, herpes simplex reactivation, neutropenia, thrombocytopenia, serum sickness (arthralgia, chills, fever and pain), headache, hypertension, diarrhoea, rash, arthralgia, pyrexia, chills, pain, oedema, abnormal liver function tests and renal function tests, cytokine release syndrome (chest pain, chills, fever dyspnoea, oedema, hypotension and tachypnoea), hyperglycaemia, haemolysis, hypotension, paraesthesia, convulsions, syncope, proteinuria.

Interactions with other medicines (*indicates serious): *upadacitinib , *Vaccines

Notes:

» Skin test: Initially perform an epicutaneous test with undiluted drug. If the subject does not show a wheal ten minutes after pricking, proceed to intradermal testing with 0.02 ml of a saline dilution (1:1000 v/v) of the drug with a separate saline control injection of similar volume. Read the result in 10 minutes. A wheal at the drug site of 3 millimetres or larger in diameter than that at the saline control site (or a positive prick test) suggests clinical sensitivity and an increased possibility of a systemic allergic reaction.

» Premedication: It is recommended to administer pre-medication with corticosteroids, antihistamines, and antipyretics prior to infusion of the drug.

» Administration: Diluted drug should be at room temperature (20°C - 25°C) prior to infusion. The drug should be administered into a high flow central vein with a recommended infusion time of not less than 4 hours. Increasing the infusion duration may minimise adverse reactions.

Azathioprine

ATC code: L04AX01

Tablet (scored), 50 mg, LOU 5

Indications and dose

Adult

Administered on expert advice.

Rheumatoid arthritis, oral: Initially 1.5–2.5 mg/kg daily in divided doses, adjusted according to response, maintenance dose, 1–3 mg/kg daily, consider withdrawal if no improvement within 3 months

Severe acute Crohn's disease, maintenance of remission of Crohn's disease, maintenance of remission of acute ulcerative colitis, oral: 2–2.5 mg/kg daily; some patients may respond to lower doses

Rheumatoid arthritis that has not responded to other disease-modifying drugs, severe SLE and other connective tissue disorders, polymyositis in cases of corticosteroid resistance, oral: Initially up to 2.5 mg/kg daily in divided doses, adjusted according to response, rarely more than 3 mg/kg daily, maintenance 1–3 mg/kg daily, consider withdrawal if no improvement within 3 months

Autoimmune conditions, oral: 1–3 mg/kg daily, adjusted according to response, consider withdrawal if no improvement within 3 months, oral administration preferable

Suppression of transplant rejection, oral: 1–2.5 mg/kg daily, adjusted according to response, oral administration preferable

Severe refractory eczema, normal or high thiopurine methyltransferase (TPMT) activity, oral: 1–3 mg/kg daily

Severe refractory eczema, intermediate TPMT activity, oral: 0.5–1.5 mg/kg daily

Generalised myasthenia gravis, oral: Initially 0.5–1 mg/kg daily, then increased to 2–2.5 mg/kg daily, dose is increased over 3–4 weeks

Paediatric

Organ transplantation, oral

Child 1 month–12 years: Initially 3–5 mg/kg once daily beginning at the time of transplant, maintenance 1–3 mg/kg once daily, adjusted according to response; total daily dose may alternatively be given in two divided doses

Contraindications: Hypersensitivity to azathioprine or mercaptopurine.

Precautions: Liver disease, renal impairment. Monitor for toxicity throughout treatment, full blood counts necessary every week (or more frequently with higher doses and in renal or hepatic impairment) for first 4 weeks of treatment, and at least every 3 months thereafter.

Patients with genetic deficiency of the enzyme thiopurine methyltransferase (TPMT) which metabolizes azathioprine are at greater risk of myelosuppressive effects.

Bone marrow suppression Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example unexplained bruising or bleeding, infection.

Renal impairment:

- Mild: dose as in normal renal function.
- Moderate: 75–100% of normal dose.
- Severe: 50–100% of normal dose.

Hepatic impairment: May need dose reduction.

Adverse effects: Common: Leukopenia, thrombocytopenia, anaemia, increased susceptibility to infections due to immunosuppression, alopecia, diarrhoea, anorexia, nausea and vomiting, mouth ulcers, oesophagitis.

Hepatitis, photosensitivity.

Rare: Hepatic veno-occlusive disease, hypersensitivity reactions, malaise, dizziness, fever, muscular pains, arthralgia, rash, hypotension or interstitial nephritis call for immediate withdrawal, cholestatic jaundice, colitis in patients also receiving corticosteroids, pancreatitis, pneumonitis, increased incidence of malignancies and lymphoproliferative disorders.

Interactions with other medicines (*indicates serious):

* Allopurinol: effects of azathioprine enhanced and toxicity increased, reduce dose of azathioprine.

Phenytoin: possibly reduced absorption of phenytoin.

* Sulfamethoxazole + trimethoprim: increased risk of haematological toxicity.

* Trimethoprim: increased risk of haematological toxicity.

* Live vaccines: avoid use of live vaccines with azathioprine (impairment of immune response).

* Warfarin: anticoagulant effect possibly reduced.

Notes:

- Also referred to as AZT (Note: this abbreviation is also used for zidovudine).
- IV injection is alkaline and very irritant, the IV route should therefore only be used if oral administration is not possible. For IV injection give over at least 1 minute. For IV infusion dilute to a concentration of 0.25–2.5 mg/mL in glucose 5% or sodium chloride 0.9% or sodium chloride and glucose, give over 30–60 minutes.
- In generalized myasthenia gravis azathioprine is usually started at the same time as the corticosteroid and allows a lower maintenance dose of the corticosteroid to be used, oral administration preferable,
- Patient information Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example unexplained bruising or bleeding, infection.
- Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.
- Hazardous agent Azathioprine is an immunosuppressive agent. Use appropriate precautions for handling and disposal.

Basiliximab

ATC code: L04AC02

Powder for injection, 20 mg, LOU 6

Indications and dose

Adult

Prophylaxis of acute rejection in allogeneic renal transplantation used in combination with ciclosporin and corticosteroid-containing immunosuppression regimens (specialist use only), by IV injection or IV infusion: Initially 20 mg, administered within 2 hours before transplant surgery, followed by 20 mg after 4 days, dose to be administered after surgery, withhold second dose if severe hypersensitivity or graft loss occurs

Paediatric

Prophylaxis of acute rejection in allogeneic renal transplantation used in combination with ciclosporin and corticosteroid-containing immunosuppression regimens (specialist use only) by IV injection or IV infusion

Child 1–17 years (body weight up to 35 kg): Initially 10 mg, dose to be administered within 2 hours before transplant surgery, followed by 10 mg after 4 days, dose administered after transplant surgery, withhold second dose if severe hypersensitivity or graft loss occurs

Child 1–17 years (body weight 35 kg and above): Initially 20 mg, administered within 2 hours before transplant surgery, followed by 20 mg after 4 days, dose to be administered after surgery, withhold second dose if severe hypersensitivity or graft loss occurs

Precautions: Off-label use in cardiac transplantation—increased risk of serious cardiac adverse effects

Conception and contraception: Adequate contraception must be used during treatment and for 16 weeks after last dose

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Anaemia, capillary leak syndrome, constipation, cytokine release syndrome, diarrhoea, dyspnoea, electrolyte imbalance, headache, heart failure, hypercholesterolaemia, hypersensitivity, hypertension, hypotension, increased risk of infection, MI, nausea, pain, peripheral oedema, post procedural wound complication, pulmonary oedema, respiratory disorders, skin reactions, sneezing, tachycardia, weight increased

Interactions with other medicines: monoclonal antibodies. Not significant.

Notes

- Basiliximab is a monoclonal antibody that acts as an interleukin-2 receptor antagonist and prevents T-lymphocyte proliferation
- DIRECTIONS FOR ADMINISTRATION: For IV infusion. give intermittently in glucose 5% or sodium chloride 0.9%, reconstitute 10 mg with 2.5 mL water for injections then dilute to at least 25 mL with infusion fluid, reconstitute 20 mg with 5 mL water for injections then dilute to at least 50 mL with infusion fluid, give over 20–30 minutes.
- Basiliximab, when used as part of an immunosuppressive regimen that includes a calcineurin inhibitor, is recommended as an initial option to prevent organ rejection in adults having a kidney transplant. The use of basiliximab with tacrolimus is outside the terms of the marketing authorisation. If this combination is prescribed, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented

Cyclosporin (Ciclosporin)

ATC code: L04AA01

Capsule, 25 mg, LOU 6

Capsule, 100 mg, LOU 6

Concentrate for injection: 50 mg/mL in 1-mL amp for organ transplantation, LOU 6

Indications and dose

Adult

Organ transplantation, oral: 10–15 mg/kg 4–12 hours before surgery, then 10–15 mg/kg daily for 1–2 weeks, reducing to 2–6 mg/kg daily for maintenance (adjust dose according to blood ciclosporin concentration and kidney function).

Organ transplantation, by IV infusion over 2–6 hours: one-third of the corresponding dose oral

Bone marrow transplantation, graft-versus-host disease, oral: 12.5–15 mg/kg daily for 2 weeks, starting on the day before surgery, followed by 12.5 mg/kg daily for 3–6 months, then gradually tailed off (may take up to 1 year after transplant)

Bone marrow transplantation, graft-versus-host disease, by IV infusion over 2–6 hours: 3–5 mg/kg daily for 2 weeks, starting on the day before surgery, followed by maintenance oral

Nephrotic syndrome, oral: Initially 5 mg/kg daily in 2 divided doses, slowly reduced to lowest effective dose according to proteinuria and serum creatinine measurements for maintenance; discontinue after 3 months if no improvement (after 6 months in membranous glomerulonephritis)

Paediatric

Notes: Lower doses are required when ciclosporin is used with other immunosuppressants. Serum level monitoring is required; a guide (based on adult recommendations) is provided in Notes; however, specialist transplant protocols should be consulted.

Solid organ transplantation, oral

Child over 3 months: 10–15 mg/kg 4–12 hours before surgery, then 10–15 mg/kg/day in 1–2 doses for 1–2 weeks, reducing to 2–6 mg/kg/day in 1–2 doses for maintenance (adjust dose according to blood ciclosporin concentration and kidney function)

Solid organ transplantation, by IV

Child over 3 months: 3–5 mg/kg 4–12 hours before surgery, then 3–5 mg/kg/day in 1–2 doses for 1–2 weeks, reducing to 0.6–2 mg/kg/day for maintenance (adjust dose according to blood ciclosporin concentration and kidney function)

Bone marrow transplantation or graft-versus-host disease (GVHD), oral

Child over 3 months: 12.5–15 mg/kg daily for 2 weeks, starting on day before transplantation (or at the onset of GVHD), followed by 12.5 mg/kg/day in 1–2 doses for 3–6 months, then gradually tailed off (may take up to 1 year after transplant)

Bone marrow transplantation or graft-versus-host disease (GVHD), IV

Child over 3 months: 3–5 mg/kg/day in 1–2 doses for 2 weeks, starting on the day before transplantation (or at the onset of GVHD), followed by oral maintenance doses

Nephrotic syndrome, oral

Child all ages: 3 mg/kg/dose twice daily. In renal impairment, initial dose should not exceed 2.5 mg/kg/day. For maintenance treatment, slowly reduce to lowest effective dose according to whole blood ciclosporin concentrations, proteinuria, and serum creatinine measurements. Discontinue after 3 months if no improvement (after 6 months in membranous glomerulonephritis).

Contraindications: Hypersensitivity to ciclosporin or any component of formulations (e.g., polyoxyl 35 castor oil in injection or polyoxyl 40 hydrogenated castor oil in capsules), breastfeeding.

Precautions: Monitor kidney function (dose-dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction, exclude rejection if kidney transplant), monitor liver function (adjust dosage according to bilirubin and liver enzymes), monitor blood pressure (discontinue if hypertension cannot be controlled by antihypertensives), monitor serum potassium, particularly if marked renal impairment (risk of hyperkalaemia), monitor serum magnesium, hyperuricaemia, measure blood lipids before and during treatment, avoid in porphyria.

Additional cautions in nephrotic syndrome: Reduce dose by 25–50% if serum creatinine more than 30% above baseline at more than one measurement, perform renal biopsies at yearly intervals, contraindicated in uncontrolled infections and malignancy.

Renal impairment: Monitor kidney function, dose-dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction (exclude rejection if kidney transplant).

Hepatic impairment: May need dose adjustment based on bilirubin or liver enzyme levels.

Adverse effects: Common: Nephrotoxicity (dose-related and reversible increases in serum creatinine and urea unrelated to tissue rejection), gingival hyperplasia, hirsutism, headache, tremor, burning sensation in hands and feet during initial therapy, electrolyte disturbances including hyperkalaemia, hypomagnesaemia, hepatic dysfunction, hyperuricaemia, hypercholesterolaemia, hyperglycaemia, hypertension (especially in heart transplant patients), increased incidence of malignancies and lymphoproliferative disorders, increased susceptibility to infections due to immunosuppression, increased insulin requirements, diabetes. GI disturbances, fatigue, myopathy or muscle weakness, gout. Rare: Confusion, coma, psychosis, allergic reactions, thrombocytopenia (sometimes with haemolytic uraemic syndrome), also mild anaemia, seizures, neuropathy, dysmenorrhoea or amenorrhoea, pancreatitis.

Interactions with other medicines (*indicates serious):

Aciclovir: increased risk of nephrotoxicity.

Allopurinol: plasma ciclosporin concentration possibly increased (risk of nephrotoxicity).

* Amikacin: increased risk of nephrotoxicity.

* Amiloride: increased risk of hyperkalaemia.

* Amphotericin B: increased risk of nephrotoxicity.

* Azithromycin: plasma concentration of ciclosporin possibly increased.

* Carbamazepine: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).

* Chloroquine: increased plasma ciclosporin concentration (increased risk of toxicity).

* Ciprofloxacin: increased risk of nephrotoxicity.

* Contraceptives, oral: plasma ciclosporin concentration increased by progestogens and possibly increased by estrogens.

* Digoxin: increased plasma concentration of digoxin (increased risk of toxicity).

* Doxorubicin: increased risk of neurotoxicity.

* Doxycycline: possibly increased plasma ciclosporin concentration.

* Enalapril: increased risk of hyperkalaemia.

* Erythromycin: increased plasma ciclosporin concentration (inhibition of metabolism of ciclosporin).

Etoposide: possibly increased plasma concentration of etoposide (increased risk of toxicity).

* Fluconazole: metabolism of ciclosporin inhibited (increased plasma concentration).

* Gentamicin: increased risk of nephrotoxicity.

* Grapefruit juice: increased plasma ciclosporin concentration (risk of toxicity).

Griseofulvin: plasma ciclosporin concentration possibly reduced.

Hydrochlorothiazide: increased risk of nephrotoxicity and possibly hypermagnesaemia.

*ibuprofen: increased risk of nephrotoxicity.

* Levofloxacin: increased risk of nephrotoxicity.

* Levonorgestrel: inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration).

* Medroxyprogesterone: inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration).

* Methotrexate: increased toxicity.

* Metoclopramide: plasma ciclosporin concentration increased.

* Nelfinavir: possibly increased plasma ciclosporin concentration.

* Norethisterone: inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration).

* Ofloxacin: increased risk of nephrotoxicity.

* Phenobarbital: metabolism of ciclosporin accelerated (reduced effect).

* Phenytoin: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).

* Potassium salts: increased risk of hyperkalaemia.

Prednisolone: increased plasma concentration of prednisolone.

* Rifampicin: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).

* Ritonavir: plasma concentration possibly increased by ritonavir.

* Saquinavir: plasma concentration of both ciclosporin and saquinavir increased.

* Silver sulfadiazine: increased risk of nephrotoxicity, possibly reduced plasma concentration of ciclosporin.

* Simvastatin: increased risk of myopathy.

Spironolactone: increased risk of hyperkalaemia.

Streptomycin: increased risk of nephrotoxicity.

* Sulfadiazine: plasma ciclosporin concentration possibly reduced, increased risk of nephrotoxicity.

* Sulfadoxine + pyrimethamine: increased risk of nephrotoxicity.

* Sulfamethoxazole + trimethoprim: increased risk of nephrotoxicity, plasma ciclosporin concentration possibly reduced by IV trimethoprim.

* Trimethoprim: increased risk of nephrotoxicity, plasma ciclosporin concentration possibly reduced by IV trimethoprim.

* Live vaccines: avoid use of live vaccines with ciclosporin (impairment of immune response).

* Vancomycin: increased risk of nephrotoxicity.

* Verapamil: increased plasma ciclosporin concentration.

Notes:

» Lower doses are required when ciclosporin is used with other immunosuppressants. Concentrate for infusion may contain polyethoxylated castor oil, which has been associated with anaphylaxis, observe patient for 30 minutes after starting infusion and then at frequent intervals.

» Conversion: Any conversion between brands should be undertaken very carefully, and the manufacturer's product information consulted for further advice.

» Note Concentrate for infusion may contain polyethoxylated castor oil, which has been associated with anaphylaxis, observe patient for 30 minutes after starting infusion and then at frequent intervals.

» Serum concentration monitoring Draw blood for ciclosporin measurement by venepuncture, not from a central line.

» Avoid using nonspecific assays which measure ciclosporin plus metabolites. Concentrations obtained from nonspecific assays are not interchangeable with the results from a specific assay.

» The ciclosporin concentration 2 hours after a dose (C2) correlates better with area under the curve (AUC) than the 12 hour trough concentration (C0). There is evidence to suggest that C2 is a better indicator of adequate immunosuppression.

» The following concentrations are a guide. They depend on assay technique, transplant type, time since transplant and use of other immunosuppressants. Aim for higher concentrations in the first 3 months after transplant and where rejection has occurred and lower concentrations where adverse effects are experienced.

» **Trough concentrations (C0)** Whole blood specific assay, 100–300 micrograms/L.

» **C2 concentrations** Collect sample 2 hours (± 15 minutes) after a dose of ciclosporin.

» **Recommended C2 whole blood concentrations in adults** Liver transplant: 600–1000 micrograms/L.

» Kidney transplant: 800–1500 micrograms/L.

» **Continuous IV infusion:** Whole blood specific assay, 300–500 micrograms/L.

» Consult local protocols or specialist advice for use in children.

» IV administration advice Dilute injection to 1:20 to 1:100 in glucose 5% or sodium chloride 0.9%, infuse IV over 2–6 hours (more slowly if facial flushing occurs), use a glass bottle and non-PVC administration set to avoid phthalate stripping and use short giving sets to reduce amount adsorbed.

» Patient information Swallow capsules whole and take them 12 hours apart at the same times each day.

» Clean your teeth and gums regularly.

» Hazardous agent Ciclosporin is an immunosuppressive agent. Use appropriate precautions for handling and disposal.

Cyclophosphamide

ATC code: L01AA01

Powder for injection, 500 mg in vial, LOU 5

Powder for injection, 1 g in vial, LOU 5

Indications and dose

Adult

Severe systemic rheumatoid arthritis, other connective tissue diseases (especially with active vasculitis, by IV injection: 0.5–1 g every 2 weeks, then reduced to 0.5–1 g every month, frequency adjusted according to clinical response and haematological monitoring; to be given with prophylactic mesna

Paediatric

High-dose conditioning for bone marrow transplantation, lupus nephritis, by IV infusion

Child: Consult local specialist protocols.

Steroid-sensitive nephrotic syndrome, by IV infusion

Child 3 months–17 years: 500 mg/m2 once a month for 6 months

Contraindications: Haemorrhagic cystitis, pregnancy, breastfeeding.

Precautions: Renal impairment, hepatic impairment, bone marrow suppression. Avoid contact with skin. May cause infertility (see Adverse effects).

Renal impairment: Reduce dose in moderate to severe impairment.

- » Mild: dose as in normal renal function.
- » Moderate: 75–100% of normal dose depending on clinical indication and local protocol.
- » Severe: 50–100% of normal dose depending on clinical indication and local protocol.

Hepatic impairment: Reduce dose.

Adverse effects: Common: Alopecia, nausea, vomiting, anorexia, haemorrhagic cystitis (see below), nasal congestion (with rapid injection), leukopenia (nadir at 8–15 days), impairment of fertility (may be irreversible), gonadal suppression (amenorrhoea). Hyperpigmentation of skin and nails, metallic taste, loss of taste. Rare: Heart failure (acute onset days after high-dose treatment, more common in older adult patients and those previously exposed to anthracyclines, may be reversible), pulmonary fibrosis (with long-term treatment), hepatic veno-occlusive disease (high dose), water retention resembling SIADH resulting in hyponatraemia and seizures (more common in high doses). Haemorrhagic cystitis: Occurs as a result of accumulation of active metabolites in the bladder. Symptoms range from mild irritation on voiding to life-threatening haemorrhagic cystitis. Patients should be advised to drink plenty of fluids during therapy, void frequently, and avoid taking the drug at night. IV hydration may be required. Mesna (not included on the 2nd WHO Model list of essential medicines for children) may be used. Toxicity is caused by the metabolite acrolein, mesna reacts specifically with acrolein in the urinary tract, preventing toxicity, mesna is given for the same duration as cyclophosphamide. It is generally given intravenously, the dose of mesna is equal to or greater than that of cyclophosphamide, often 125%.

Interactions with other medicines (*indicates serious):

* Allopurinol: increases the myelotoxicity of cyclophosphamide.

Carbamazepine: may increase conversion of cyclophosphamide to active metabolites.

* Chloramphenicol: reduced cyclophosphamide effectiveness.

* Ciclosporin: decreased ciclosporin concentration.

* Hydrochlorothiazide: increased myelotoxicity of cyclophosphamide.

* Ondansetron: reduced cyclophosphamide effectiveness.

Phenytoin: possibly reduced absorption of phenytoin.

Phenobarbital: may increase conversion of cyclophosphamide to active metabolites.

Suxamethonium: enhanced effect of suxamethonium.

Vaccines, live: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

* Warfarin: increased INR and increased risk of bleeding.

Notes:

- » Handle as a cytotoxic

Everolimus

ATC code: L04AA18

Tablet, 500 micrograms (or 0.5 mg), LOU 5

Indications and dose

Adult

Liver transplantation, oral: Initially 1 mg twice daily, to be started approximately 4 weeks after transplantation; maintenance dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

Renal transplantation, heart transplantation, oral: Initially 750 micrograms twice daily, to be started as soon as possible after transplantation; maintenance dose adjusted according to response and whole blood everolimus concentration; dose adjustments can be made every 4–5 days

Paediatric

Consult product literature

Precautions: History of bleeding disorders, peri-surgical period (impaired wound healing)

Conception and contraception: Effective contraception must be used during and for up to 8 weeks after treatment.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Hepatic impairment: No or insufficient data on the pharmacokinetics of this drug in hepatic impairment. Therefore, uptitration should be done with caution.

Adverse effects: Common or very common: Alopecia, anaemia, appetite decreased, arthralgia, asthenia, cough, decreased leucocytes, dehydration, diabetes mellitus, diarrhoea, dry mouth, dyslipidaemia, dysphagia, dyspnoea, electrolyte imbalance, eye inflammation, fever. GI discomfort. haemorrhage, headache, hyperglycaemia, hypertension, increased risk of infection, insomnia, menstrual cycle irregularities, mucositis, nail disorders, nausea, neutropenia, oral disorders, peripheral oedema, proteinuria, renal impairment, respiratory disorders, skin reactions, taste altered, thrombocytopenia, vomiting, weight decreased. Uncommon: Congestive heart failure, embolism, and thrombosis, flushing,

healing impaired, hepatitis B, musculoskeletal chest pain, pancytopenia, sepsis, urinary frequency increased. Rare or very rare: Pure red cell aplasia. Frequency not known: hepatitis B reactivation

Interactions with other medicines:

- Everolimus potentially increases the risk of angioedema when given with ACEIs.
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin,) are predicted to decrease the concentration of everolimus. Avoid or adjust dose.
- Antifungals, azoles (fluconazole, ketoconazole, itraconazole) are predicted to increase the concentration of everolimus. Avoid or adjust dose.
- CCBs (diltiazem, verapamil) are predicted to increase the concentration of everolimus. Avoid or adjust dose.
- Ciclosporin moderately increases the exposure to everolimus. Avoid or adjust dose.
- Efavirenz is predicted to decrease the concentration of everolimus. Avoid or adjust dose
- HIV-protease inhibitors are predicted to increase the concentration of everolimus. Avoid.
- Macrolides (erythromycin, clarithromycin) are predicted to increase the concentration of everolimus. Avoid
- Nevirapine is predicted to decrease the concentration of everolimus. Avoid or adjust dose.
- Rifampicin is predicted to decrease the concentration of everolimus. Avoid or adjust dose.

Notes:

- Everolimus is a protein kinase inhibitor.
- Reduce dose or discontinue if severe adverse effects occur—consult product literature.
- MONITORING REQUIREMENTS: manufacturer advises everolimus blood concentration monitoring is required— consult product literature. Manufacturer advises monitor blood-glucose concentration, CBC, serum-triglycerides and serum-cholesterol before treatment and periodically thereafter.
- Monitor renal function before treatment and periodically thereafter.
- Monitor for signs and symptoms of infection before and during treatment.
- DIRECTIONS FOR ADMINISTRATION DISPERSIBLE TABLETS: Manufacturer advises tablets must be dispersed in water before administration— consult product literature for details. After solution has been swallowed, any residue must be re-dispersed in the same volume of water and swallowed.
- PRESCRIBING AND DISPENSING INFORMATION: Everolimus is available as both tablets and dispersible tablets. These formulations vary in their licensed indications and are not interchangeable—consult product literature for information on switching between formulations.
- PATIENT AND CAREGIVER ADVICE: Pneumonitis Non-infectious pneumonitis reported. Manufacturer advises patients and their Caregivers should be informed to seek urgent medical advice if new or worsening respiratory symptoms occur. Infections Manufacturer advises patients and their Caregivers should be informed of the risk of infection.

Methylprednisolone

ATC code: H02AB04

Powder for injection, 125 mg (as sodium succinate),

LOU 4

Powder for injection, 500 mg (as sodium succinate),

LOU 4

Indications and dose

Adult

Suppression of inflammatory and allergic disorders, cerebral oedema associated with malignancy by slow IV injection or IV infusion: Initially 10–500 mg

*Graft rejection reactions by IV infusion***:** Up to 1 g daily for up to 3 days

*Relapse in multiple sclerosis when oral steroids have failed or have not been tolerated, or in those who require hospital admission, by IV infusion***:** 1 g once daily for 3–5 days

Paediatric

Inflammatory and allergic disorders, by slow IV injection or IV infusion

Child: 0.5–1.7 mg/kg daily in 2–4 divided doses, divide doses depending on condition and response

Graft rejection reactions, by IV injection

Child: 10–20 mg/kg once daily for 3 days, alternatively 400–600 mg/m2 once daily (max. per dose 1 g) for 3 days

Severe erythema multiforme, lupus nephritis, systemic onset juvenile idiopathic arthritis, by IV injection

Child: 10–30 mg/kg once daily or on alternate days (max. per dose 1 g) for up to 3 doses

Precautions: With IV use: Rapid IV administration of large doses associated with cardiovascular collapse. With systemic use: Systemic sclerosis (increased incidence of scleroderma renal crisis)

Adverse effects: Common or very common: With parenteral use Confusion, delusions, depressed mood, diarrhoea, dizziness, dyslipidaemia, hallucination, hiccups, Kaposi's sarcoma, lipomatosis, oedema, schizophrenia, suicidal thoughts, vomiting, withdrawal syndrome

Interactions → corticosteroids

- Antiepileptics (phenobarbital, phenytoin, carbamazepine) increase exposure to methylprednisolone
- Protease inhibitors increase exposure to methylprednisolone
- Macrolides (Erythromycin, Clarithromycin) increase exposure to methylprednisolone
- Antifungals (fluconazole, miconazole, ketoconazile) increase concentration of methylprednisolone

» High dose aspirin, NSAIMs increase the risk of GIT bleeding with corticosteroids

» Rifampicin decreases exposure to methylprednisolone

Notes: Methylprednisolone exerts predominantly glucocorticoid effects with minimal mineral corticoid effects

Mycophenolic Acid

ATC code: L04AA06

Tablet (e/c), 180 mg (as mycophenolate sodium), LOU 6

Tablet (e/c), 360 mg (as mycophenolate sodium), LOU 6

Indications and dose

Renal transplantation (specialist use only), oral: 720 mg twice daily, to be started within 72 hours of transplantation

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Precautions: Active serious GI disease (risk of haemorrhage, ulceration and perforation). children (higher incidence of adverse effects may call for temporary reduction of dose or interruption). delayed graft function, elderly (increased risk of infection, GI haemorrhage and pulmonary oedema). increased susceptibility to skin cancer (avoid exposure to strong sunlight).risk of hypogammaglobulinaemia or bronchiectasis when used in combination with other immunosuppressants. *For Hypogammaglobulinaemia or bronchiectasis:* Measure serum immunoglobulin levels if recurrent infections develop, and consider bronchiectasis or pulmonary fibrosis if persistent respiratory symptoms such as cough and dyspnoea develop.

Adverse effects: Common or very common: Anxiety, burping, confusion, dizziness, gout, hepatic disorders, hyperbilirubinaemia, hyperuricaemia, neuromuscular dysfunction, taste altered, vasodilation. Acidosis, alopecia, anaemia, appetite decreased, arthralgia, asthenia, bone marrow disorders, chills, constipation, cough, depression, diarrhoea, drowsiness, dyslipidaemia, dyspnoea, electrolyte imbalance, fever, GI discomfort, GI disorders, GI haemorrhage, headache, hyperglycaemia, hypertension, hypotension, increased risk of infection, insomnia, leucocytosis, leucopenia, malaise, nausea, neoplasms, oedema, oral disorders, pain, pancreatitis, paraesthesia, renal impairment, respiratory disorders, seizure, sepsis, skin reactions, tachycardia, thinking abnormal, thrombocytopenia, tremor, vomiting, weight decreased. Uncommon: Agranulocytosis. Frequency not known: Endocarditis, hypogammaglobulinaemia, malignancy, meningitis, neutropenia, polyomavirus-associated nephropathy, progressive multifocal leukoencephalopathy, pure red cell aplasia. Cases of pure red cell aplasia have been reported with mycophenolate mofetil, dose reduction or discontinuation should be considered under specialist supervision.

Interactions with other medicines:

» Increased risk of haematological toxicity with acyclovir, gancyclovir

» Antacid decrease exposure to mycophenolate

» Rifampicin decreases concentration of mycophenolate

Notes:

» Mycophenolic acid 720 mg is approximately equivalent to mycophenolate mofetil 1 g but avoid unnecessary switching because of pharmacokinetic differences

» Exclude pregnancy in females of child-bearing potential before treatment—2 pregnancy tests 8–10 days apart are recommended. Women should use at least 1 method of effective contraception before and during treatment, and for 6 weeks after discontinuation—2 methods of effective contraception are preferred. Male patients or their female partner should use effective contraception during treatment and for 90 days after discontinuation

» IMPORTANT SAFETY INFORMATION/ADVICE: MYCOPHENOLATE MOFETIL, MYCOPHENOLIC ACID: UPDATED CONTRACEPTION ADVICE FOR MALE PATIENTS: Available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate medicines, however mycophenolate mofetil and mycophenolic acid are genotoxic and a risk cannot be fully excluded.

Mycophenolate Mofetil

ATC code: L04AA06

Tablet, 250 mg, LOU 6

Tablet, 500 mg, LOU 6

Indications and dose

Prophylaxis of acute rejection in renal transplantation (in combination with a corticosteroid and ciclosporin) (under expert supervision), oral: 1 g twice daily, to be started within 72 hours of transplantation

Prophylaxis of acute rejection in cardiac transplantation (in combination with ciclosporin and corticosteroids) (under expert supervision), oral: 1.5 g twice daily, to be started within 5 days of transplantation

Paediatric

Prophylaxis of acute rejection in renal transplantation (in combination with a corticosteroid and ciclosporin) (under expert supervision), oral

Child: 600 mg/m2 twice daily, consult local protocol for details, maximum 2 g per day

Prophylaxis of acute rejection in renal transplantation (in combination with a corticosteroid and tacrolimus) (under expert supervision), oral

Child: 300 mg/m2twice daily, consult local protocol for details, maximum 2 g per day

Prophylaxis of acute rejection in hepatic transplantation (in combination with a corticosteroid and ciclosporin or tacrolimus) (under expert supervision), oral

Child: 10 mg/kg twice daily, increased to 20 mg/kg twice daily, consult local protocol for details, maximum 2 g per day

Precautions: Active serious GI disease (risk of haemorrhage, ulceration and perforation). children

(higher incidence of adverse effects may call for temporary reduction of dose or interruption). delayed graft function, elderly (increased risk of infection, GI haemorrhage and pulmonary oedema). increased susceptibility to skin cancer (avoid exposure to strong sunlight). Risk of hypogammaglobulinaemia or bronchiectasis when used in combination with other immunosuppressants. For hypogammaglobulinaemia or bronchiectasis: Measure serum immunoglobulin levels if recurrent infections develop, and consider bronchiectasis or pulmonary fibrosis if persistent respiratory symptoms such as cough and dyspnoea develop.

Adverse effects: Common or very common: Anxiety, burping, confusion, dizziness, gout, hepatic disorders, hyperbilirubinaemia, hyperuricaemia, neuromuscular dysfunction, taste altered, vasodilation. Acidosis, alopecia, anaemia, appetite decreased, arthralgia, asthenia, bone marrow disorders, chills, constipation, cough, depression, diarrhoea, drowsiness, dyslipidaemia, dyspnoea, electrolyte imbalance, fever, GI discomfort, GI disorders, GI haemorrhage, headache, hyperglycaemia, hypertension, hypotension, increased risk of infection, insomnia, leucocytosis, leucopenia, malaise, nausea, neoplasms, oedema, oral disorders, pain, pancreatitis, paraesthesia, renal impairment, respiratory disorders, seizure, sepsis, skin reactions, tachycardia, thinking abnormal, thrombocytopenia, tremor, vomiting, weight decreased. Uncommon: Agranulocytosis. Frequency not known: Endocarditis, hypogammaglobulinaemia, malignancy, meningitis, neutropenia, polyomavirus-associated nephropathy, progressive multifocal leukoencephalopathy, pure red cell aplasia. Cases of pure red cell aplasia have been reported with mycophenolate mofetil, dose reduction or discontinuation should be considered under specialist supervision.

Interactions

- Increased risk of haematological toxicity with acyclovir, gancyclovir
- Antacid decrease exposure to mycophenolate
- Rifampicin decreases concentration of mycophenolate

Notes:

- Mycophenolic acid 720 mg is approximately equivalent to mycophenolate mofetil 1 g but avoid unnecessary switching because of pharmacokinetic differences
- Exclude pregnancy in females of child-bearing potential before treatment—2 pregnancy tests 8–10 days apart are recommended. Women should use at least 1 method of effective contraception before and during treatment, and for 6 weeks after discontinuation—2 methods of effective contraception are preferred. Male patients or their female partner should use effective contraception during treatment and for 90 days after discontinuation
- IMPORTANT SAFETY INFORMATION/ADVICE: MYCOPHENOLATE MOFETIL, MYCOPHENOLIC ACID: UPDATED CONTRACEPTION ADVICE FOR MALE PATIENTS Available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate medicines, however mycophenolate mofetil and mycophenolic acid are genotoxic and a risk cannot be fully excluded.

Prednisolone

Indication and Dose

Adult

Rheumatoid Arthritis, Oral: 5-7.5 mg Daily

Multiple Sclerosis, Oral: 200 mg/day for 1 week, then 80 mg every other day for 1 month

Paediatric

Nephrotic Syndrome, Oral: First 4 weeks: 60 mg/m²/day or 2 mg/kg/day PO divided q8hr until urine is protein free for 3 consecutive days; not to exceed 28 days; dose not to exceed 80 mg/day.

Subsequent 4 weeks: 40 mg/m² or 1-1.5 mg/kg PO every other day; not to exceed 80 mg/day.

Maintenance in frequent relapses: 0.5-1 mg/kg/dose PO every other day for 3-6 months

Treatment may have to be individualized.

For ATC code, strenght, contraindications, precautions, use in hepatic impairment, pregnancy, breastfeeding, adverse effects, interactions with other medicines and notes See 9.2.4

Rituximab

ATC code L01XC02

Injection (IV), 10 mg/mL (10-mL vial), LOU 6

Injection (IV), 10 mg/mL (50-mL vial), LOU 6

Indications and dose

Adult

Rheumatoid arthritis (specialist use only), by IV infusion: 1 g, then 1 g after 2 weeks

Pemphigus vulgaris (specialist use only), by IV infusion: 1 g, then 1 g after 2 weeks, maintenance 0.5 g, at months 12 and 18, and then every 6 months thereafter if needed; consult product literature for treatment of relapse

Paediatric: sed in *Rheumatology see section 28*

Contraindications: Severe infection, when used for granulomatosis with polyangiitis and microscopic polyangiitis, pemphigus vulgaris, or rheumatoid arthritis, severe heart failure, severe, uncontrolled heart disease

Precautions: History of cardiovascular disease, exacerbation of angina, arrhythmia, and heart failure have been reported, patients receiving cardiotoxic chemotherapy, exacerbation of angina, arrhythmia, and heart failure have been reported, pre-medication recommended to minimise adverse reactions (consult product literature). predisposition to infection. transient hypotension occurs frequently during infusion (antihypertensives may need to be withheld

for 12 hours before infusion):

When used for granulomatosis with polyangiitis and microscopic polyangiitis, or pemphigus vulgaris Pneumocystis jirovecii pneumonia—consult product literature for prophylaxis requirements

Adverse effects: Common or very common: Angioedema, anxiety, appetite decreased, arrhythmias, bone marrow disorders, bursitis, cancer pain, cardiac disorder, chest pain, chills, dizziness, dysphagia, dyspnoea, ear pain, electrolyte imbalance, GI discomfort, GI disorders, hepatitis B, hypercholesterolaemia, hyperglycaemia, hyperhidrosis, hypertension, hypotension, insomnia, lacrimation disorder, malaise, migraine, multi organ failure, muscle complaints, muscle tone increased, nausea, nerve disorders, oedema, oral disorders, osteoarthritis, respiratory disorders, sensation abnormal, sepsis, skin reactions, throat irritation, tinnitus, vasodilation, weight decreased. Uncommon: Asthma, coagulation disorder, heart failure, hypoxia, ischaemic heart disease, lymphadenopathy, taste altered. Rare or very rare: Cytokine release syndrome, facial paralysis. renal failure, SJS (discontinue). toxic epidermal necrolysis (discontinue). tumour lysis syndrome, vasculitis, vision disorders. Frequency not known: Epistaxis, hearing loss, hypogammaglobulinaemia, infective thrombosis, influenza like illness, irritability, muscle weakness, nasal congestion, posterior reversible encephalopathy syndrome, psychiatric disorder, seizure, skin papilloma, tremor

Interactions with other medicines : monoclonal antibodies. Not significant

Notes: Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking rituximab. Patients with positive hepatitis B serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation, treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for up to a year following the last infusion (consult product literature).

Tacrolimus

ATC code: L04AD02

Concentrate (for IV infusion), 5 mg/1-mL amp, LOU 6

Capsule 500 micrograms, LOU 6

Capsule, 1 mg, LOU 6

Capsule, 5 mg, LOU 6

Indications and dose

Adult

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation, oral: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation, oral: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation, oral: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation, oral: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation when oral route not appropriate, by IV infusion: Initially 10–50 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation when oral route not appropriate, by IV infusion: Initially 50–100 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation, by IV infusion: Initially 10–20 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation, by IV infusion: Initially 10–20 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Allograft rejection resistant to conventional immunosuppressive therapy, by continuous IV infusion: Seek specialist advice, consult local protocol

Paediatric

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation, oral

Neonate: Initially 150 micrograms/kg twice daily

Child: Initially 150 micrograms/kg twice daily

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation, oral

Neonate: Initially 150 micrograms/kg twice daily.

Child: Initially 150 micrograms/kg twice daily, a lower initial dose of 100 micrograms/kg twice daily has been used in adolescents to prevent very high 'trough' concentrations

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation, oral

Neonate: Initially 50–150 micrograms/kg twice daily.

Child: Initially 50–150 micrograms/kg twice daily

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation, oral

Neonate: Initially 150 micrograms/kg twice daily, dose to be given as soon as clinically possible (8–12 hours after discontinuation of IV infusion).

Child: Initially 150 micrograms/kg twice daily, dose to be given as soon as clinically possible (8–12 hours after discontinuation of IV infusion)

Allograft rejection resistant to conventional immunosuppressive therapy, oral

Child: Seek specialist advice

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation when oral route not appropriate, by continuous IV infusion

Neonate: Initially 50 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours.

Child: Initially 50 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation when oral route not appropriate, by continuous IV infusion

Neonate: Initially 75–100 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours.

Child: Initially 75–100 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation, by continuous IV infusion

Neonate: Initially 30–50 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours.

Child: Initially 30–50 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Allograft rejection resistant to conventional immunosuppressive therapy, by continuous IV infusion

Child: Seek specialist advice (consult local protocol)

Precautions Increased risk of infections, lymphoproliferative disorders, malignancies, neurotoxicity, QT-interval prolongation, UV light (avoid excessive exposure to sunlight and sunlamps)

Adverse effects: Common or very common: Alopecia, anaemia, anxiety, appetite decreased, arrhythmias, ascites, asthenic conditions, bile duct disorders, confusion, consciousness impaired, constipation, coronary artery disease, cough, depression, diabetes mellitus, diarrhoea, dizziness, dysgraphia, dyslipidaemia, dyspnoea, electrolyte imbalance, embolism and thrombosis, eye disorder. febrile disorders, fluid imbalance, GI discomfort. GI disorders, GI inflammatory disorders, haemorrhage, hallucination, headache, hepatic disorders, hyperglycaemia, hyperhidrosis, hypertension, hyperuricaemia, hypotension, increased risk of infection, ischaemia, joint disorders, leucocytosis, leucopenia, metabolic acidosis, mood altered, muscle spasms, nasal complaints, nausea, nephropathy, nervous system disorder, oedema, oral disorders, pain, peripheral neuropathy, peripheral vascular disease, primary transplant dysfunction, psychiatric disorder, renal impairment, renal tubular necrosis, respiratory disorders, seizure, sensation abnormal, skin reactions, sleep disorders, temperature sensation altered, thrombocytopenia, tinnitus, tremor, urinary tract disorder, urine abnormal, vision disorders, vomiting, weight changes. Uncommon: Asthma, cardiac arrest. cardiomyopathy, cataract, CNS haemorrhage, chest discomfort, coagulation disorders, coma, dysmenorrhoea, encephalopathy, feeling abnormal, haemolytic anaemia, hearing impairment, heart failure, hypoglycaemia, hypoproteinaemia, influenza like illness, memory loss, multi organ failure, neutropenia, palpitations, pancreatitis, pancytopenia, paralysis, paresis, photosensitivity reaction, psychotic disorder, shock, speech disorder, stroke, ventricular hypertrophy. Rare or very rare: Fall, hirsutism, mobility decreased, muscle tone increased, muscle weakness, pancreatic pseudocyst, pericardial effusion, QT interval prolongation, SCARs, sinusoidal obstruction syndrome, thirst, ulcer. Frequency not known: Agranulocytosis, neoplasm malignant, neoplasms, polyomavirus-associated nephropathy, progressive multifocal leukoencephalopathy, pure red cell aplasia. Specific adverse effects with IV use: Anaphylactoid reaction (due to excipient), hypersensitivity. Cardiomyopathy has been reported to occur primarily in children with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Patients should be monitored by echocardiography for hypertrophic changes—consider dose reduction or discontinuation if these occur.

Interactions with other medicines:

Increased concentration of tacrolimus:

- Antifungals: ketoconazole, fluconazole
- Antiarrythmics: Amiodarone
- CCBs: diltiazem, verapamil
- Ciclosporin
- Grapefruit
- Protease Inhibitors
- Macrolides: clarithromycin, erythromycin
- Decreased concentration of tacrolimus:
- Antiepileptics: carbamazepine, phenytoin, phenobarbitone
- Efavirenz, Nevirapine
- Rifampicin
- St Johns wort (*Hypericum perforatum*)

Notes:

- Tacrolimus is a calcineurin inhibitor
- Dose equivalence and conversion: IV and oral doses are not interchangeable due to differences in bioavailability. Follow correct dosing recommendations for the dosage form when switching formulations
- Important safety information: oral tacrolimus products: prescribe and dispense by brand name only, to minimize the risk of inadvertent switching between products, which has been associated with reports of toxicity and graft rejection.
- Directions for administration: with IV use for IV infusion: give continuously in glucose 5% or sodium chloride 0.9%. Dilute concentrate in infusion fluid to a final concentration of 4–100 micrograms/mL, give over 24 hours. Tacrolimus is incompatible with PVC.
- Patient and Caregiver advice: avoid excessive exposure to UV light including sunlight. Driving and skilled tasks may affect performance of skilled tasks (e.g., Driving).

9.2. Antineoplastic & Supportive Medicines

9.2.1. Cytotoxic Medicines

Arsenic Trioxide

ATC code: L01XX27

Concentrate solution for infusion, 1 mg/mL, LOU 6

Indications and dose

Adult

Acute promyelocytic leukaemia (specialist use only) by IV infusion: Consult product literature or local protocols

Precautions: Hypokalaemia (correct before treatment), hypomagnesaemia (correct before treatment), previous treatment with anthracyclines (increased risk of QT interval prolongation)

Breastfeeding: discontinue breastfeeding.

Renal impairment manufacturer advises caution—limited information available.

Hepatic impairment manufacturer advises use with caution—no information available.

Adverse effects: Common or very common: Abdominal pain, alveolar haemorrhage, anaemia, arrhythmias, arthralgia, chest pain, chills, diarrhoea, differentiation syndrome, dizziness, dyspnoea, electrolyte imbalance, fatigue, fever, headache, hyperbilirubinaemia, hyperglycaemia, hypotension, hypoxia, increased risk of infection, ketoacidosis, leucocytosis, myalgia, nausea, neutropenia, oedema, pain, pancytopenia, paraesthesia, pericardial effusion, QT interval prolongation. renal failure, respiratory disorders, seizure, skin reactions, thrombocytopenia, vasculitis, vision blurred, vomiting, weight increased. Frequency not known: Confusion, decreased leucocytes, encephalopathy, fluid imbalance, heart failure, hepatotoxicity, peripheral neuropathy, sepsis. Signs and symptoms of differentiation syndrome (leucocyte activation syndrome) include unexplained fever, dyspnoea, weight gain, pulmonary infiltrates, pleural or pericardial effusions, with or without leucocytosis—treat with high dose corticosteroids, consult product literature.

Interactions with other medicines: Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, carboplatin, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.

Notes: Monitoring requirements ECG required before and during treatment—consult product literature

Bendamustine

ATC code L01AA09

Injection, 100 mg/20-mL vial, LOU 5

Indications and dose

Adult

*Chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, multiple myeloma by IV infusion***:** Consult local protocols

Paediatric: No dosing recommendations available

Contraindications: Jaundice, low leucocyte count, low platelet count, major surgery less than 30 days before start of treatment, severe bone marrow suppression

Precautions Cardiac disorders—monitor serum potassium and ECG

Pregnancy Avoid (teratogenic and mutagenic in animal studies).

Breastfeeding: Discontinue breastfeeding

Hepatic/Renal impairment: No or insufficient data on the pharmacokinetics of this drug in renal/hepatic impairment. Therefore uptitration should be done with caution.

Adverse effects: Common or very common: Alopecia, amenorrhoea, anaemia, angina pectoris, appetite decreased, arrhythmias, cardiac disorder, chills, constipation, decreased leucocytes, dehydration, diarrhoea, dizziness, fatigue, fever, haemorrhage, headache, hepatitis B reactivation, hypersensitivity, hypertension, hypokalaemia, hypotension, increased risk of infection, insomnia, mucositis, nausea, neutropenia, pain, palpitations, respiratory disorders, skin reactions, stomatitis, thrombocytopenia, tumour lysis syndrome, vomiting. Uncommon: Bone marrow disorders, heart failure, MI, neoplasms, pericardial effusion. Rare or very rare: Anticholinergic syndrome, aphonia, ataxia, circulatory collapse, drowsiness, haemolysis, hyperhidrosis, infertility, multi organ failure, nervous system disorder. paraesthesia, peripheral neuropathy, sepsis. taste altered. Frequency not known: Extravasation necrosis, hepatic failure, necrosis. renal failure, SCARs.

Secondary malignancy: Use of bendamustine

is associated with an increased incidence of acute leukaemias.

Infections: Serious and fatal infections are reported, including opportunistic infections such as Pneumocystis jirovecii pneumonia, varicella zoster virus and CMV—manufacturer advises monitoring for respiratory signs and symptoms throughout treatment, patients should be advised to report new signs of infection, including fever or respiratory symptoms, promptly. Reactivation of hepatitis B is reported in patients who are chronic carriers of the virus—manufacturer advises monitoring for signs and symptoms of active hepatitis B during treatment and for several months after stopping treatment.

Interactions with other medicines: alkylating agents

- Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, carboplatin, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.
- Increased risk of nephrotoxicity on concurrent use with other nephrotoxic agents including: Aceclofena, acyclovir, amikacin, amphotericin, bacitracin, capreomycin, carboplatin, cephalexin, cefixime, ceftazidime, ciclosporin, cisplatin, dexketoprofen, diclofenac, etoricoxib, ganciclovir, gentamicin, ibuprofen, gentamicin, ketoprofen, mefenamic acid, indomethacin, meloxicam, methotrexate, oxaliplatin, piroxicam, streptomycin, tacrolimus, trimethoprim, vancomycin, tenofovir disoproxil, zidovudine, zoledronate.

Notes

- IMPORTANT SAFETY INFORMATION: BENDAMUSTINE: INCREASED MORTALITY OBSERVED IN CLINICAL STUDIES IN OFFLABEL USE, MONITOR FOR OPPORTUNISTIC INFECTIONS, HEPATITIS B REACTIVATION. Clinical trials have shown increased mortality when bendamustine was used in combination treatments outside its approved indications. Risk of opportunistic infections for all patients receiving bendamustine treatment may be greater than previously recognized. It is recommended that patients be monitored for opportunistic infections as well as cardiac, neurological, and respiratory adverse events, known carriers of HBV should be monitored for signs and symptoms of active HBV infection. Patients should be advised to report promptly new signs of infection, consider discontinuing bendamustine if there are signs of opportunistic infections.
- Effective contraception is required during treatment in men or women, and for 6 months after treatment in men.

Bleomycin

ATC code: L01DC01

Powder for injection, 15 mg (as sulphate) in vial, LOU 5

Indications and dose

Adjunct to surgery and radiotherapy in palliative treatment of Hodgkin and non-Hodgkin lymphomas; carcinomas of the head, neck, larynx, cervix, penis, skin, vulva, and testicles, including embryonal cell carcinoma, choriocarcinoma and teratoma, malignant effusions, Kaposi sarcoma: Consult specialist protocols. Maximum cumulative dose for adults is 300 000–400 000 units.

Note: Doses of bleomycin are expressed in units; 1 bleomycin Unit in the USP is equivalent to 1000 units.

Paediatric: Consult specialist protocols

Contraindications: Acute pulmonary infection or significantly reduced lung function, allergy to bleomycin, pregnancy, breastfeeding.

Precautions: Renal impairment, pulmonary impairment.

Renal impairment: Monitor plasma creatinine at baseline and before each cycle.

- Mild: dose as in normal renal function.
- Moderate: 75% of normal dose (100% for malignant effusions).
- Severe: 50% of normal dose (100% for malignant effusions).

Hepatic impairment: Dosage reduction not necessary.

Adverse effects: Common: Rash, erythema, itch, vesiculation, hyperkeratosis, hyperpigmentation (particularly of skin folds), nail changes, oral mucositis, alopecia, fever and chills (usually occur within 4–10 hours of a dose and last 4–12 hours or longer), hypersensitivity (see below), pulmonary toxicity (see below), nausea and vomiting. Uncommon: Raynaud phenomenon. Rare: Acute chest pain during infusion.

Hypersensitivity: Occurs in about 1% of lymphoma patients but otherwise appears to be rare. Usually presents with hypotension, high fever, chills, confusion and wheezing. May be immediate or delayed and usually occurs with the first or second dose.

Pulmonary toxicity: Occurs in approximately 10% of patients, initial symptoms include dyspnoea, cough and sometimes fever. Pneumonitis may progress to pulmonary fibrosis and death. Onset may be delayed for up to 6 months after the last dose. Risk factors include high cumulative dose, mediastinal radiotherapy, renal impairment, pre-existing lung disease and oxygen supplementation. Stop bleomycin if pneumonitis is suspected. Corticosteroids are used although evidence is limited.

Interactions with other medicines (*indicates serious):

- *Cisplatin: increased pulmonary toxicity.
- *Oxygen: serious pulmonary toxicity in patients exposed to conventional oxygen concentrations during anaesthesia.
- Phenytoin: possibly reduced absorption of phenytoin.

- Vaccines, live: avoid use of live vaccines with bleomycin (impairment of immune response).
- *Vinblastine: increased risk of cardiovascular toxicity.
- Digoxin: bleomycin may decrease digoxin absorption.
- Amphotericin B: concurrent bleomycin may increase nephrotoxicity and risk of hypotension and bronchospasm.

Notes:

- No single monitoring test reliably predicts bleomycin pulmonary toxicity, monitoring may include:
- Chest X-ray at baseline, then each week during and for 4 weeks after treatment, pulmonary function tests (particularly total lung volume and forced vital capacity),
- Baseline and monthly evaluation of carbon monoxide diffusion capacity, stop treatment if it falls to < 30–35% of pretreatment value.
- 1500 IU of bleomycin are equivalent to 1.5 USP bleomycin units and approximately 1.5 mg (by potency) or 1 mg (by weight). Caution is required when converting from mg to IU as protocols or trials may state bleomycin doses in terms of mg-potency rather than mg-weight.
- Irritant to tissues, needs to be administered with care.
- Handle as a cytotoxic

Cabazitaxel

ATC code: L01CD04

Injection, 60mg (1.5-mL vial), LOU 5

Indications and dose

Adult

Hormone-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen

Intravenous infusion: 20mg/m2 once every 3 weeks in combination with oral prednisolone or Prednisolone 10mg daily throughout treatment. Select patients may use 25mg/m2 at the clinicians' discretion.

Dosage modifications for toxicity

If at 20 mg/m2: Reduce to 15 mg/m2

If at 25 mg/m2: Reduce to 20 mg/m2; additional dose reduction to 15 mg/m2 may be considered. (Limited data on doses below 20 mg/m2).

Neutropenia

- Grade ≥3 neutropenia greater than 1 week despite appropriate G-CSF treatment: Delay treatment until absolute neutrophil count >1,500 cells/mm3, then reduce dose by one dose level with continued GCSF secondary prophylaxis.
- Febrile neutropenia or neutropenic infection: Delay treatment until improvement or resolution, and until absolute neutrophil count >1,500 cells/mm3, then reduce dose by one dose level with continued GCSF secondary prophylaxis.

Diarrhoea

- Grade ≥3 diarrhoea or persisting diarrhoea despite appropriate treatment, including fluid and electrolytes replacement: Delay treatment until resolution or improvement then reduce dose by one dose level.

Peripheral neuropathy

- Grade 2: Delay treatment until improvement or resolution, then reduce dose by one dose level
- Grade >3: Discontinue treatment.

Paediatric

There is no relevant use in the paediatric population.

The safety and the efficacy in children and adolescents below 18 years of age have not been established.

Contraindications: Hypersensitivity to the active substance to other taxanes, or polysorbate 80 or any excipients, neutrophil counts less than 1,500/mm3, Severe hepatic impairment (total bilirubin >3 x ULN), Concomitant vaccination with yellow fever vaccine.

Precautions:

- Hypersensitivity reactions: severe hypersensitivity reactions can occur and include generalised rash, hypotension and bronchospasms can occur. Immediate discontinuation is required if hypersensitivity is severe with administration of appropriate supportive medications. All patients should be premedicated prior to the initiation of the infusion of cabazitaxel (see notes).
- Bone marrow suppression manifested as neutropenia, anaemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported. Primary prophylaxis with GCSF is recommended in patients with high-risk clinical features (older patients, poor nutrition status, other major comorbidities, poor performance status).
- Gastrointestinal toxicity: Nausea, vomiting, and severe diarrhoea may occur. Rehydrate and treat with antiemetics and antidiarrheals as needed; incidence of gastrointestinal adverse reactions is greater in patients with a prior history of pelvic radiation or gastrointestinal disease.
- GI haemorrhage and perforation, ileus, enterocolitis with fatal outcome have been reported; risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, antiplatelets, or anticoagulants, and prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding.
- Pulmonary toxicity: Interstitial pneumonitis and acute respiratory distress syndrome have been observed. Patients with underlying pulmonary disease are at highest risk. May require discontinuation of treatment.
- Renal failure: Renal failure has been reported and has been associated with dehydration,

sepsis or obstructive uropathy. Adequate hydration should be ensured throughout treatment. Treatment should be discontinued in case of any degradation of renal function to renal failure ≥CTCAE 4.0 Grade 3.

» Cardiac arrhythmias risk: Cardiac arrhythmias have been reported, most commonly tachycardia and atrial fibrillation.

Hepatic impairment:

» Mild impairment (total bilirubin> 1 to ≤1.5 times upper limit normal or or Aspartate Aminotransferase (AST) ≥1.5 x ULN): Administer 20 mg/m2 and monitor closely.

» Moderate impairment (total bilirubin> 1.5 to ≤3 times upper limit normal and any AST): Administer 15 mg/m2 (limited efficacy data are available at this dose).

» Severe hepatic impairment (total bilirubin >3 x ULN) Use is contraindicated.

Renal impairment:

» Creatinine clearance ≥15 ml/minute: No dose adjustment required.

» Creatinine clearance <15 ml/minute and end stage renal disease: Use with caution and monitor closely.

Pregnancy: should not be used during pregnancy. Men should use effective non oral contraception during treatment and for at least 4 months after discontinuation of treatment.

Breastfeeding: Not recommended for use during breastfeeding.

Adverse effects: Neutropenic sepsis, anaemia, thrombocytopenia, leukopenia, diarrhoea, nausea, vomiting, dysgeusia, dry mouth, stomatitis, ileus, colitis, peripheral neuropathy, fatigue, headache, conjunctivitis, tinnitus, atrial fibrillation, hypertension, hypotension, deep vein thrombosis, pneumonia, alopecia, myalgia, arthralgia, renal failure.

Interactions with other medicines (*indicates serious): *CYP3A4 inhibitors (strong) - examples: ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, ritonavir voriconazole - Concurrent use should be avoided; consider a 25% dose reduction of therapy if concurrent use unavoidable.

*CYP3A4 inducers (strong)- examples: phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St John's Wort - concurrent use should be avoided.

Organic Anion Transport Polypeptides (OATP1B1)- examples: statins, valsartan, repaglinide - A time interval of 12 hours is recommended before the infusion and at least 3 hours after the end of infusion before administering the OATP1B1 substrates.

Vaccines: the effectiveness of the vaccines could be reduced.

Notes:

» Premedication with an antihistamine, corticosteroids, H2 antagonists and antiemetics 30minutes prior to administration of the drug should be given.

Calcium Folinate (Calcium Leucovorin, Folinic Acid or Leucovorin)

ATC code: V03AF03

Injection, 3 mg/mL in 10-mL amp, 10 mg/mL (5-mL vial, 30-mL vial), LOU 5

Tablet: 15 mg, LOU 5

Indications and dose

Adult

Colorectal Carcinoma, IV or IV infusion: Various protocols depending on treatment regimen (Refer to treatment protocols

Methotrexate Overdose, IV: (Administer as soon as possible and within 24 hr methotrexate level is >10-6 M or 48 hour level is >9 x 10-7 M), the dose of leucovorin should be increased to 100 mg/m2 IV every 3 hours until methotrexate level is <10-8 M.

» **Note:** Hydration (3 L/day) and urinary alkalinization with sodium bicarbonate solution should be employed concomitantly; bicarbonate dose should be adjusted to maintain urine pH at 7.0 or greater

High Dose Methotrexate Rescue, IV: 10 mg/m² IV every 6 hours for 10 doses; starts 24 to 36 hours after beginning of methotrexate infusion (refer to treatment protocol).

May give oral tablets after 1st IV dose.

Doses adjusted as follows:

Normal methotrexate elimination:

» Serum methotrexate level approximately 10 micromolar, 24 hr after administration, 1 micromolar at 48 hr, <0.2 micromolar at 72 hr

» Administer 15 mg oral, IM, or IV every 6 hours for 60 hours (10 doses starting at 24 hr after start of methotrexate infusion

Delayed late methotrexate elimination:

» Serum methotrexate level remaining above 0.2 micromolar at 72 hr, and more than 0.05 micromolar at 96 hr after administration.

» Continue 15 mg oral, IM, or IV every 6 hours, until methotrexate level <0.05 micromolar

Delayed early methotrexate elimination and/or evidence of acute renal injury.

» Serum methotrexate level of 50 micromolar or more at 24 hr, or 5 micromolar or more at 48 hr after administration, or a 100% or greater increase in serum creatinine level at 24 hr after methotrexate administration (e.g., increase from 0.5 mg/dL to a level of 1 mg/dL or more)

» Administer 150 mg IV every 3 hours until methotrexate level is <1 micromolar; then 15 mg IV every 3 hours until methotrexate level is <0.05 micromolar.

Paediatric

Methotrexate Overdose, High Dose Methotrexate Rescue

Follow adult dosing

Contraindications: Intrathecal injection of calcium folinate is contraindicated.

Precautions: Not for use in patients with pernicious

anaemia or other megaloblastic anaemias due to vitamin B12 deficiency. Avoid simultaneous administration of methotrexate.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Allergic reactions, fever. Rare: Seizures, fainting.

Interactions with other medicines (*indicates serious):

Phenobarbital: plasma concentration of phenobarbital possibly reduced.

Phenytoin: plasma phenytoin concentration possibly reduced.

Fluorouracil: toxicity enhanced but used for this purpose intentionally.

Trimethoprim: reduced therapeutic effect.

Notes:

- In presence of gastrointestinal toxicity, nausea or vomiting, calcium folinate should be administered parenterally.
- **NOT** to be administered intrathecally.
- serum creatinine and methotrexate levels should be determined at least once daily.
- Administration, hydration, and urinary alkalization (pH of 7.0 or greater) should be continued until methotrexate level is below 5 x 10-8 M (0.05 micromolar)

Capecitabine

ATC code: L01BC06

Tablet, 150 mg, LOU 5

Tablet, 500 mg, LOU 5

Indications and dose

Adult

Stage III colon cancer, adjuvant following surgery (monotherapy), oral:: 1.25 g/m2 twice daily for 14 days, subsequent courses repeated after a 7-day interval, recommended duration of treatment is 6 months, adjust dose according to tolerability—consult product literature

Stage III colon cancer, adjuvant following surgery (combination therapy), oral: 0.8–1 g/m2 twice daily for 14 days, subsequent courses repeated after a 7-day interval, recommended duration of treatment is 6 months, adjust dose according to tolerability—consult product literature

Metastatic colorectal cancer (monotherapy) oral: 1.25 g/m2 twice daily for 14 days, subsequent courses repeated after a 7-day interval, adjust dose according to tolerability—consult product literature

Metastatic colorectal cancer (combination therapy), oral: 0.8–1 g/m2twice daily for 14 days, subsequent courses repeated after a 7-day interval, adjust dose according to tolerability—consult product literature

Advanced gastric cancer (first-line treatment in combination with a platinum based regimen), oral: 0.8–1 g/m2 twice daily for 14 days, subsequent courses repeated after a 7-day interval, alternatively 625 mg/m2 twice daily given continuously, adjust dose according to tolerability—consult product literature

Locally advanced or metastatic breast cancer (second-line treatment as monotherapy after failure of a taxane and anthracycline regimen or where further anthracycline treatment is not indicated), locally advanced or metastatic breast cancer (second-line treatment, in combination with docetaxel, where previous therapy included an anthracycline), oral: 1.25 g/m2 twice daily for 14 days, subsequent courses repeated after a 7-day interval, adjust dose according to tolerability—consult product literature

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Dihydropyrimidine dehydrogenase deficiency, history of severe and unexpected reactions to fluoropyrimidine therapy, hypersensitivity to capecitabine or to any of the excipients or fluorouracil, during pregnancy and breastfeeding, in patients with: severe leukopenia, neutropenia, or thrombocytopenia, severe hepatic impairment, severe renal impairment (CrCl below 30 mL/min), recent or concomitant treatment with brivudine. If contraindications exist to any of the medicinal products in the combination regimen, that medicinal product should not be used.

Precautions: Diabetes mellitus, diarrhoea or dehydration— consult product literature for guidance on dose modification and treatment interruption, electrolyte disturbances, history of angina pectoris, history of arrhythmias, history of significant cardiovascular disease, nervous system disease

Conception and contraception: contraceptive advice required.

Pregnancy: avoid (teratogenic in animal studies).

Breastfeeding: discontinue breastfeeding.

Hepatic impairment: monitor liver function in mild-to-moderate dysfunction—consult product literature for guidance on treatment interruption, avoid in severe impairment.

Renal impairment avoid if CrCl less than 30 mL/min.

Dose adjustments: reduce starting dose of 1.25 g/m2 to 75% if CrCl 30–50 mL/min.

Adverse effects: abdominal pain, vomiting, diarrhea, weakness, and rashes, blood clotting problems, allergic reactions, heart problems such as cardiomyopathy low blood cell counts. Common or very common: Alopecia, anaemia, appetite abnormal, asthenia, chest pain, constipation, cough, dehydration, depression, diarrhoea, dizziness, dry mouth, dyspnoea, embolism and thrombosis, eye disorders, eye inflammation, eye irritation, fever. GI discomfort. GI disorders, haemorrhage, headache, hyperbilirubinaemia, increased risk of infection, insomnia, joint disorders, lethargy, malaise, nail disorder. nausea, neutropenia, oedema, pain, rhinorrhoea, sensation abnormal, skin reactions, stomatitis. taste altered, vomiting, weight decreased. Uncommon: Acute coronary syndrome, aphasia, arrhythmias, ascites, asthma, chills, confusion, diabetes mellitus, dysphagia, ear pain, facial swelling, haemolytic anaemia, hepatic disorders, hot flush, hydronephrosis, hypertension, hypertriglyceridaemia, hypokalaemia, hypotension, influenza like illness, ischaemic heart disease, leucopenia, libido decreased, lipoma, malnutrition, memory loss, movement

disorders, muscle weakness, musculoskeletal stiffness, palpitations, pancytopenia, panic attack, peripheral coldness, peripheral neuropathy, photosensitivity reaction, pneumothorax. radiation recall reaction, sepsis, skin ulcer. syncope. thrombocytopenia, urinary disorders, vertigo, vision disorders. Rare or very rare: Cutaneous lupus erythematosus, encephalopathy, QT interval prolongation, SCARs, vasospasm. Frequency not known: Cardiomyopathy, heart failure, sudden death

Interactions with other medicines:

- Phenytoin: increased phenytoin plasma concentrations resulting in symptoms of phenytoin intoxication in single cases have been reported during concomitant use of capecitabine with phenytoin. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- Allopurinol: interactions with allopurinol have been observed for 5-FU, with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine should be avoided.
- Coumarins: Capecitabine increases the effects of coumarins. Monitor INR and adjust dose.
- Metronidazole: Increases risk of capecitabine toxicity on coadministration.
- Increased risk of *myelosuppression* on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, carboplatin, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.

Notes:

- Capecitabine is metabolized to fluorouracil
- Monitoring requirements: monitor plasma-calcium concentration. monitor for eye disorders (including keratitis and corneal disorders). severe skin reactions monitor for symptoms of severe skin reactions (including SJS and toxic epidermal necrolysis)—permanently discontinue treatment immediately if symptoms occur. hand-foot syndrome: monitor for symptoms of hand-foot syndrome—interrupt treatment if significant syndrome occurs and refer to product literature.

Carboplatin

ATC code: L01XA02

Injection, 10 mg/mL solution, 15 mL and 45 mL, LOU 5

Indications and dose

Adult

Stage 4 neuroblastoma, germ cell tumours, low-grade gliomas (including astrocytomas), neuroectodermal tumours (including medulloblastoma), rhabdomyosarcoma (metastatic and non-metastatic disease), soft tissue sarcomas, retinoblastoma, high-risk Wilms tumour, some liver tumours: See specialist treatment protocols.

Dose is frequently calculated according to the individual patient's renal function and ability to clear the drug.

Calvert formula for carboplatin dosing in adults:

Total dose (mg) = target AUC (mg.minute/mL) × [GFR (mL/min) + 25].

Paediatric

See specialist treatment protocols.

Dose is frequently calculated according to the individual patient's renal function and ability to clear the drug.

Modified Calvert formula for children:

Total dose (mg) = [target AUC (mg.minute/mL)] × [GFR (mL/min) + (0.36 × body weight in kg)].
Contraindications: Hypersensitivity to carboplatin, cisplatin, other platinum containing compounds or mannitol, severe bone marrow suppression or excessive bleeding, pregnancy, breastfeeding.

Precautions: Renal impairment.

Renal impairment: Renal function is often factored into dose calculations for carboplatin. If renally adjusted doses are not being used and the patient is renally impaired, consider reducing dose and monitor haematological parameters and renal function, avoid if CrCl less than 20 mL/min.

Hepatic impairment: Dosage reduction not necessary.

Adverse effects: Common: Myelosuppression (see below), nausea, vomiting, peripheral neuropathy, taste abnormality, fatigue, hypersensitivity reactions including anaphylaxis (risk increases with repeated exposure), reversible elevation of serum creatinine, mild and reversible electrolyte abnormalities (hyponatraemia, hypokalaemia, hypocalcaemia, hypomagnesaemia), mild elevations of ALP, liver transaminases and bilirubin, alopecia, myalgia, weakness. Ototoxicity, abdominal pain, diarrhoea, constipation, oral mucositis. Rare: Acute renal failure, haemolytic uraemic syndrome, loss of vision (at higher than usually recommended doses).

Myelosuppression: Major dose-limiting effect. Thrombocytopenia is more common and pronounced than leukopenia, it may be cumulative and sometimes requires platelet transfusion. Nadir of platelet and neutrophil counts occurs 14–28 days after a dose, with recovery usually within 28 days. Anaemia may be cumulative and require transfusion.

Interactions with other medicines

- Phenytoin: decreased serum levels of phenytoin.
- Digoxin: reduced absorption of digoxin.
- Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, cisplatin, chlorambucil, cyclophosphamide, docetaxel,

doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.

» Increased risk of nephrotoxicity on concurrent use with other nephrotoxic agents including: Aceclofena, acyclovir, amikacin, amphotericin, bacitracin, capreomycin, carboplatin, cephalexin, cefixime, ceftazidime, ciclosporin, cisplatin, dexketoprofen, diclofenac, etoricoxib, ganciclovir, gentamicin, ibuprofen, gentamicin, ketoprofen, mefenamic acid, indomethacin, meloxicam, methotrexate, oxaliplatin, piroxicam, streptomycin, tacrolimus, trimethoprim, vancomycin, tenofovir disoproxil, zidovudine, zoledronate.

» Increased risk of ototoxicity on concurrent use with other ototoxic agents including: Amikacin, cisplatin, furosemide, gentamicin, oxaliplatin, torsemide, vincristine, vinblastine, vancomycin.

» Increased risk of peripheral neuropathy on concurrent use with other agents causing it, including: Cisplatin, docetaxel, isoniazid, lamivudine, metronidazole, nitrofurantoin, paclitaxel, phenytoin, stavudine, vincristine, vinblastine, thalidomide.

Notes:

» This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance.

» Needle or IV administration sets containing aluminium parts should not be used in the administration or preparation of carboplatin as an interaction may cause precipitate formation and loss of potency.

Chlorambucil

ATC code: L01AA02

Tablet, 2 mg, LOU 5

Adult

Indications and dose

Non-Hodgkin lymphomas, Hodgkin disease, histiocytosis, and Waldenstrom (primary) macroglobulinaemia: Consult specialist protocols.

Paediatric: Consult specialist protocols

Contraindications: Hypersensitivity to chlorambucil or any component, cross-hypersensitivity (skin rash) may occur with other alkylating agents

Precautions: Severe hepatic impairment, renal impairment, seizure disorders, bone marrow suppression, effective contraception is advised in both men and women, affects fertility (see Adverse effects). Reduce initial dose if a patient has received radiation therapy, myelosuppressive drugs, or has reduced baseline leukocyte or platelet count within the previous 4 weeks.

Renal impairment: Moderate or severe: use with caution and monitor response, increased risk of myelosuppression. Dose reduction not usually necessary.

Hepatic impairment: Consider dose reduction in severe hepatic impairment.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Common: Rash, dose-limiting myelosuppression (nadir 14 days), transient elevations in liver enzymes. Abdominal discomfort, diarrhoea, oral mucositis.

Rare: Hallucinations, seizures, sterile cystitis, hepatotoxicity, jaundice, severe pneumonitis, SJS, toxic epidermal necrolysis, drug fever, irreversible bone marrow suppression, pulmonary fibrosis, tremor, peripheral neuropathy, sterility in pre-pubertal and pubertal males (less likely in females).

Interactions with other medicines (*indicates serious):

Phenytoin: possibly reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with chlorambucil (impairment of immune response).

Phenobarbital: increased toxicity of chlorambucil.

Notes:

» Tablets should be swallowed whole on an empty stomach and not broken, chewed or crushed.

» Avoid the need to cut tablets by using different doses on alternate days.

» Store tablets at 2–8 °C (36–46 °F). Tablets may be stored at room temperatures up to 30 °C (86 °F) for up to 1 week.

Cisplatin

ATC code: L01XA01

Injection, 1 mg/mL (50-mL vial), LOU 5

Indications and dose

Adult

Metastatic testicular tumours, metastatic ovarian tumours, advanced bladder carcinoma and other solid tumours, including lung, cervical, and head and neck cancers: Consult specialist literature.

Paediatric: Not licenced for use in children

Contraindications: consult specialist literature

Precautions: consult specialist literature

Renal impairment: Avoid.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant

therefore its use is not recommended.

Adverse effects: see note above and consult specialist literature

Interactions with other medicine:

- Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.
- Increased risk of nephrotoxicity on concurrent use with other nephrotoxic agents including: Aceclofenac, acyclovir, amikacin, amphotericin, bacitracin, capreomycin, carboplatin, cephalexin, cefixime, ceftazidime, ciclosporin, dexketoprofen, diclofenac, etoricoxib, ganciclovir, gentamicin, ibuprofen, gentamicin, ketoprofen, mefenamic acid, indomethacin, meloxicam, methotrexate, oxaliplatin, piroxicam, streptomycin, tacrolimus, trimethoprim, vancomycin, tenofovir disoproxil, zidovudine, zoledronate.
- Increased risk of ototoxicity on concurrent use with other ototoxic agents including: Amikacin, furosemide, gentamicin, oxaliplatin, torsemide, vincristine, vinblastine, vancomycin.
- Increased risk of peripheral neuropathy on concurrent use with other agents causing it, including: Docetaxel, isoniazid, lamivudine, metronidazole, nitrofurantoin, paclitaxel, phenytoin, stavudine, vincristine, vinblastine, thalidomide.
- Increased risk of pulmonary toxicity with bleomycin.

Cyclophosphamide

ATC code: L01AA01

Powder for injection, 500 mg in vial, LOU 5

Powder for injection, 1 g in vial, LOU 5

Tablet, 50 mg, LOU 5

Indications and dose

Adult

Severe systemic rheumatoid arthritis, other connective tissue diseases (especially with active vasculitis, by IV injection: 0.5–1 g every 2 weeks, then reduced to 0.5–1 g every month; frequency adjusted according to clinical response and haematological monitoring; to be given with prophylactic mesna

Used mainly in combination with other agents for treating a wide range of malignancies, including some leukaemias, lymphomas, and solid tumours, by IV infusion: Consult local specialist protocols for dosing schedules.

Paediatric

Acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, retinoblastoma, neuroblastoma, rhabdomyosarcoma, soft-tissue sarcomas, Ewing tumour, neuroectodermal tumours (including medulloblastoma), infant brain tumours, ependymona, high-dose conditioning for bone marrow transplantation, lupus nephritis, by IV infusion: Consult local specialist protocols.

Steroid-sensitive nephrotic syndrome, by IV infusion

Child 3 months–17 years: 500 mg/m2 once a month for 6 months

Contraindications: Haemorrhagic cystitis, pregnancy, breastfeeding.

Precautions: Renal impairment, hepatic impairment, bone marrow suppression. Avoid contact with skin. May cause infertility (see Adverse effects)

Renal impairment: Reduce dose in moderate to severe impairment.

- Mild: dose as in normal renal function
- Moderate: 75–100% of normal dose depending on clinical indication and local protocol.
- Severe: 50–100% of normal dose depending on clinical indication and local protocol.

Hepatic impairment: Reduce dose.

Adverse effects: Common: Alopecia, nausea, vomiting, anorexia, haemorrhagic cystitis (see below), nasal congestion (with rapid injection), leukopenia (nadir at 8–15 days), impairment of fertility (may be irreversible), gonadal suppression (amenorrhoea). Hyperpigmentation of skin and nails, metallic taste, loss of taste. Rare: Heart failure (acute onset days after high-dose treatment, more common in older adult patients and those previously exposed to anthracyclines, may be reversible), pulmonary fibrosis (with long-term treatment), hepatic veno-occlusive disease (high dose), water retention resembling SIADH resulting in hyponatraemia and seizures (more common in high doses).

Haemorrhagic cystitis: Occurs as a result of accumulation of active metabolites in the bladder. Symptoms range from mild irritation on voiding to life-threatening haemorrhagic cystitis. Patients should be advised to drink plenty of fluids during therapy, void frequently, and avoid taking the drug at night. IV hydration may be required. Mesna (not included on the 2nd WHO Model list of essential medicines for children) may be used. Toxicity is caused by the metabolite acrolein, mesna reacts specifically with acrolein in the urinary tract, preventing toxicity, mesna is given for the same duration as cyclophosphamide. It is generally given intravenously, the dose of mesna is equal to or greater than that of cyclophosphamide, often 125%.

Interactions with other medicines (*indicates serious):

- *Allopurinol: increases the myelotoxicity of cyclophosphamide.
- Carbamazepine: may increase conversion of cyclophosphamide to active metabolites.
- *Ciclosporin: decreased ciclosporin concentration.
- *Hydrochlorothiazide: increased myelotoxicity

of cyclophosphamide.

- *Ondansetron: reduced cyclophosphamide effectiveness.
- Phenytoin: possibly reduced absorption of phenytoin.
- Phenobarbital: may increase conversion of cyclophosphamide to active metabolites.
- Suxamethonium: enhanced effect of suxamethonium.
- Vaccines, live: avoid use of live vaccines with cyclophosphamide (impairment of immune response).
- *Warfarin: increased INR and increased risk of bleeding.

Notes: Handle as a cytotoxic

Cytarabine (Aca-C)

ATC code: L01BC01

Powder for injection, 100 mg in vial, LOU 5

Powder for injection, 1 g in vial, LOU 5

Adult

Indications and dose

Acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin lymphoma, meningeal leukaemia, meningeal neoplasms: See specialist treatment protocols.

Paediatric: See specialist treatment protocols.

Contraindications: Pregnancy, breastfeeding.

Precautions: Hepatic impairment, renal impairment.

Renal impairment: For low-dose regimens dose reductions are not necessary. For high-dose therapy the following information should be considered:

- Elevated baseline serum creatinine (> 106 micromol/L) is an independent risk factor for the development of neurotoxicity during treatment, retrospective analysis implicates impaired renal function as an independent risk factor for high-dose cytarabine-induced cerebral and cerebellar toxicity, the incidence of neurotoxicity is increased following administration of high-dose cytarabine to patients with even mildly impaired renal function.
- Suggested dose reductions for high-dose therapy in patients with renal impairment.
  - Mild: 50–60% of normal dose.
  - Moderate or severe: avoid use of cytarabine high-dose.

Hepatic impairment: Reduce dose.

Adverse effects: Common: Myelosuppression (see below), nausea, vomiting, diarrhoea, oral mucositis, rash, fever, elevated liver function tests, alopecia, ocular discomfort. Conjunctivitis, GI haemorrhage, oesophagitis, jaundice, dizziness, cellulitis at injection site, chest pain, urinary retention, renal impairment, anaphylaxis. Rare: Palmar-plantar erythrodysaesthesia, severe spinal cord toxicity following intrathecal administration.

Myelosuppression: Major dose-limiting adverse effect, includes neutropenia, thrombocytopenia and anaemia, more severe after high doses or continuous infusions. *Neutropenia* is biphasic with a nadir 7–9 days after the dose and a more severe nadir at 15–24 days. Platelet nadir is 12–15 days after dose. Recovery generally occurs after a further 10 days.

High-dose therapy: Associated with severe and sometimes fatal GI, neurological and pulmonary toxicity, adverse effects include peripheral neuropathy, cerebral and cerebellar dysfunction, cardiomyopathy, pulmonary oedema, GI ulceration. Reversible corneal toxicity leading to haemorrhagic conjunctivitis or keratitis can occur (prophylactic corticosteroid or lubricant eye drops may help).

Interactions with other medicines:

Digoxin: decreases digoxin oral tablet absorption.

Flucytosine: plasma flucytosine concentration possibly reduced.

Phenytoin: reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with cytarabine (impairment of immune response).

Notes:

- Based on weight or BSA, children may tolerate higher doses of cytarabine than adults.
- Conjunctivitis (which occurs more frequently in high-dose therapy) is preventable and treatable with a corticosteroid eye drop. As prophylaxis, eye drops should be started 6–12 hours before initiation of cytarabine and continued for 24 hours following the last dose.

Dacarbazine

ATC code: L01AX04

Powder for injection, 200 mg in vial (as citrate), LOU 5

Indications and dose

Adult

Hodgkin disease, rhabdomyosarcoma, neuroblastoma, fibrosarcomas, soft tissue sarcomas, bone marrow transplant: Consult specialist protocols.

Paediatric: Consult specialist protocols

Contraindications: Pregnancy (avoid for 6 months after treatment completed in both male and female patients), breastfeeding.

Precautions: Renal and hepatic impairment, bone marrow depression, ensure adequate contraception during and for 6 months after treatment in men and women.

Renal impairment: Mild: 75–80% of dose. Moderate to severe: 70% of dose, use with caution.

Hepatic impairment: Dose reduction may be required in mild to moderate liver disease, avoid if severe.

Adverse effects: Common: Diarrhoea, flu-like syndrome (fever, myalgia, malaise), transient increases in hepatic transaminases and ALP, facial flushing, pain along injected vein, nausea and vomiting. Agranulocytosis, blurred vision, seizures, confusion, headache, alopecia, erythematous and maculopapular rash,

photosensitivity, hypotension (infusion related). Rare: Intractable nausea and vomiting, hepatic vein thrombosis and hepatocellular necrosis, tissue damage due to extravasation.

Interactions with other medicines (*indicates serious):

Phenytoin: possibly reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with dacarbazine (impairment of immune response).

Phenobarbital: may induce dacarbazine metabolism.

Notes:

- IV infusion: For IV infusion, further dilute reconstituted solution in 125–250 mL glucose 5% or sodium chloride 0.9%, give over 15–30 minutes.
- Protect infusion set from light throughout administration to reduce pain.
- Highly irritant to tissues, inject with care.
- Handle as a cytotoxic.

Dactinomycin

ATC code: L01DA01

Powder for injection, 500 micrograms in vial, LOU 5

Indications and dose

Adult

Trophoblastic tumours, Wilms tumour, testicular tumours, Ewing sarcoma, rhabdomyosarcoma, other soft tissue sarcomas: Consult specialist protocols.

Paediatric: Consult specialist protocols.

Contraindications: Pregnancy, breastfeeding.

Precautions: Hepatic or biliary impairment, concurrent or previous radiotherapy, vesicant (extravasation during IV use can cause severe tissue damage).

Renal impairment: No dose reductions necessary.

Hepatic impairment: Consider dose reduction if raised serum bilirubin or biliary obstruction.

Adverse effects: Common: Myelosuppression (see below), nausea and vomiting, oral mucositis, oesophagitis, pharyngitis, diarrhoea, fever, malaise, myalgia, alopecia, rash, acne. Rare: Anaphylaxis, hepatotoxicity, hepatic veno-occlusive disease (common in Wilms tumour). *Myelosuppression:* Affects mainly white cells and platelets, nadir of white cell and platelet count occurs 14–21 days after dose with recovery in 21–25 days.

Interactions with other medicines

Phenytoin: possibly reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with dactinomycin (impairment of immune response).

Notes:

- Previous radiotherapy: erythema and pigmentation may recur at site of previous radiation.
- Current radiotherapy: radiation effects (including skin, GI and bone marrow toxicity) may be potentiated.
- Children may experience increased risk of toxicity and are at greater risk of hepatic veno-occlusive disease.
- Vesicant, avoid extravasation. Extremely damaging to soft tissue and will cause a severe local reaction if extravasation occurs. Administer slow IV push over 10–15 minutes. Do not give intramuscularly or subcutaneously.
- Care should be taken with units: chemotherapy protocols can list dactinomycin doses in mg (e.g., mg/kg or mg/m2), but medication orders are often written in micrograms.
- Handle as a cytotoxic.
- Highly irritant to tissues, inject with care. Also referred to as actinomycin D.

Daunorubicin

ATC code: L01DB02

Powder for injection, 20 mg (as HCl), LOU 5

Powder for injection, 50 mg (as HCl), LOU 5

Indications and dose

Adult

Acute myelogenous leukaemia, acute lymphocytic leukaemia, neuroblastoma, rhabdomyosarcoma: Consult specialist protocols.

Paediatric

Consult specialist protocols.

Maximum cumulative dose (irreversible myocardial toxicity may occur as total dosage approaches)

Child under 2 years: 10 mg/kg (300 mg/m2)

Child over 2 years: 300 mg/m2

Contraindications: Pregnancy, breastfeeding, congestive heart failure, left ventricular ejection fraction < 30–40%, arrhythmias, pre-existing bone marrow suppression.

Precautions: Hepatic and renal impairment, cardiac disease, reduced cardiac reserve or treatment with other cardiotoxic drugs, highly irritant to tissues (inject with extreme care), previous treatment to maximum cumulative dose with another anthracycline.

Renal impairment: Mild to moderate: reduce dose.

Hepatic impairment: Reduce dose according to serum bilirubin concentration, see specialist protocols for details.

Adverse effects: Common: Rash, itch, nausea, vomiting, diarrhoea, alopecia, oral mucositis, oesophagitis, myelosuppression (see below), cardiac toxicity (see below), fatigue, headache. Rare: Secondary malignancies. *Myelosuppression:* Occurs commonly, affecting white cells and to a lesser degree, platelets and red cells. The white count nadir occurs about 10 days after a dose with recovery by about 21 days.

Cardiac toxicity: May be acute, chronic or delayed. Acute toxicity (ECG changes and arrhythmias) occurs during or immediately after a dose and is not dose related. It is usually transient but may rarely result in myopericarditis and cardiac failure.

Chronic toxicity: usually occurs within a year of stopping treatment and is related to cumulative dose.

Cardiomyopathy: may result in heart failure.

Delayed toxicity: occurs years to decades after treatment and is thought to be dose related. It may present as ventricular dysfunction, heart failure, conduction disturbances or arrhythmias.

Interactions with other medicines (*indicates serious):

Phenytoin: possibly reduced absorption with phenytoin.

Vaccines, live: avoid use of live vaccines with daunorubicin (impairment of immune response).

Notes:

- Daunorubicin HCl (conventional formulation) should not be confused with daunorubicin liposomal formulation.
- Daunorubicin is a vesicant, severe local tissue necrosis will result if extravasation occurs. Do not give intramuscularly or subcutaneously.
- Give by IV injection or short infusion into a side arm of a fast running infusion to reduce the risk of irritation or extravasation.
- Monitor ECG and left ventricular ejection fraction at baseline and during treatment.

Docetaxel

ATC code L01CD02

Injection (premixed), 120 mg vial, LOU 5

Injection (premixed), 80 mg vial, LOU 5

Indications and dose

Adult

- *Adjuvant treatment of operable node-positive and operable node-negative breast cancer (in combination with doxorubicin and cyclophosphamide)*
- *Initial chemotherapy of locally advanced or metastatic breast cancer (with doxorubicin)*
- *Locally advanced or metastatic breast cancer where cytotoxic chemotherapy with an anthracycline or an alkylating drug has failed (monotherapy)*
- *Locally advanced or metastatic breast cancer where cytotoxic chemotherapy with an anthracycline has failed (with capecitabine)*
- *Initial chemotherapy of metastatic breast cancer which overexpresses human epidermal growth factor-2 (with trastuzumab)*
- *Locally advanced or metastatic non-small cell lung cancer where previous chemotherapy has failed, Initial chemotherapy of unresectable, locally advanced or metastatic non-small cell lung cancer (with cisplatin)*
- *Hormone-resistant metastatic prostate cancer (in combination with prednisone or prednisolone)*
- *Initial treatment of metastatic gastric adenocarcinoma, including adenocarcinoma of the gastro-oesophageal junction (with cisplatin and fluorouracil)*
- *Induction treatment of locally advanced squamous cell carcinoma of the head and neck (with cisplatin and fluorouracil)*

Adult dose: Consult product literature or local protocols.

Paediatric: No or insufficient experience in children and adolescents therefore its use is not recommended.

Precautions: Avoid in acute porphyrias

Hepatic impairment: caution in mild to moderate and to avoid in severe impairment. *Dose adjustments:* dose reduction according to liver function tests in mild to moderate impairment

Conception and contraception: effective contraception for men and women during treatment, and for at least 6 months after stopping treatment in men.

Breastfeeding: discontinue breastfeeding.

Adverse effects: Common or very common: Abdominal pain, alopecia, anaemia, appetite decreased, arrhythmia, arthralgia, asthenia, constipation, diarrhoea, dyspnoea, fluid imbalance, haemorrhage, hypersensitivity, hypertension, hypotension, increased risk of infection, myalgia, nail disorders, nausea, neutropenia, pain, peripheral neuropathy, sepsis, skin reactions, stomatitis, taste altered, thrombocytopenia, vomiting. Uncommon: GI disorders, heart failure. Frequency not known: Ascites, bone marrow depression, chest tightness, chills, cutaneous lupus erythematosus, disseminated intravascular coagulation, eye disorders, eye inflammation, fever. hearing impairment. hepatitis, hyponatraemia, loss of consciousness, multi organ failure, MI, nail discolouration, neurotoxicity, ototoxicity, pericardial effusion, peripheral lymphoedema, peripheral oedema, pulmonary oedema, radiation injurie, renal impairment. respiratory disorders, sclerodermal-like changes, seizure, sensation abnormal, SCARs. vasodilation, venous thromboembolism, vision disorders, weight increased

Interactions with other medicines: taxanes

- Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, cisplatin, chlorambucil, cyclophosphamide, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.
- Increased risk of peripheral neuropathy on concurrent use with other agents causing it, including: Cisplatin, isoniazid, lamivudine, metronidazole, nitrofurantoin, carboplatin, paclitaxel, phenytoin, stavudine, vincristine, vinblastine, thalidomide.
- Drugs that increase concentration of docetaxel: Antifungals: ketoconazole, fluconazole. Macrolides. Avoid or adjust dose
- Drugs that decrease concentration of docetaxel: Antiepileptics (phenobarbitone, carbamazepine, phenytoin). Rifampicin, St John's wort

Notes

- Pretreatment with dexamethasone oral is recommended for reducing fluid retention and hypersensitivity reactions.
- Monitoring monitor liver function in hepatic impairment

Doxorubicin (Adriamycin)

ATC code: L01DB01

Powder for injection or solution for injection, 50 mg (as HCl) in vial, LOU 5

Indications and dose

Adult

Malignancies, including Ewing sarcoma, osteogenic sarcoma, Wilms tumour, neuroblastoma, retinoblastoma, some liver tumours, acute lymphoblastic leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, germ cell tumours of the testis: Consult specialist protocols.

Paediatric: Consult specialist protocols.

Contraindications: Pregnancy and breastfeeding, congestive heart failure, left ventricular ejection fraction < 30–40%, arrhythmias, pre-existing bone marrow suppression.

Precautions: Avoid extravasation (highly irritant to the tissues), previous treatment to maximum cumulative dose with another anthracycline, hepatic impairment, renal impairment, cardiac disease, treatment with other cardiotoxic drugs, previous mediastinal or pericardial irradiation.

Renal impairment: Mild to moderate: use with caution, avoid excessive doses.

Severe: use 75% of normal dose, use with caution.

Hepatic impairment: Reduce dose according to serum bilirubin concentration.

- Do not use doxorubicin if bilirubin > 85 micromol/L.
- Bilirubin 20–50 micromol/L: reduce dose by 50%.
- Bilirubin > 50 micromol/L: reduce dose by 75%.

Adverse effects: Common: Rash, itch, myelosuppression (see below), cardiac toxicity (see below), red coloured urine, nausea, vomiting, stomatitis, GI ulceration.

Conjunctivitis, lacrimation and facial flushing, hyperpigmentation of nails, buccal mucosa and skin folds, fever, chills, palmar-plantar erythrodysaesthesia. Rare: Secondary malignancies.

Cardiac toxicity: May be acute, chronic or delayed. Acute toxicity (ECG changes and arrhythmias) occurs during or immediately after a dose and is not dose related. It is usually transient but may rarely result in myopericarditis and cardiac failure.

Chronic toxicity usually occurs within a year of stopping treatment and is related to cumulative dose.

Cardiomyopathy may result in heart failure.

Delayed toxicity occurs years to decades after treatment and is thought to be dose related. It may present as ventricular dysfunction, heart failure, conduction disturbances or arrhythmias.

Myelosuppression: Occurs commonly, affecting white cells and, to a lesser degree, platelets and red cells. The white cell count nadir occurs about 10 days after a dose, with recovery by about 21 days.

Interactions with other medicines (*indicates serious):

- *Ciclosporin: increased risk of neurotoxicity.
- Phenytoin: possibly reduced absorption of phenytoin.
- Phenobarbital: increases elimination of doxorubicin.
- Stavudine: doxorubicin may inhibit effect of stavudine.
- Vaccines, live: avoid use of live vaccines with doxorubicin (impairment of immune response).
- * Warfarin: increased INR and increased risk of bleeding.

Notes:

- Doxorubicin HCl (conventional formulation) should not be confused with doxorubicin liposomal formulation.
- Doxorubicin is a vesicant, severe local tissue necrosis will result if extravasation occurs.
- Do not give intramuscularly or subcutaneously.
- Monitor ECG and left ventricular ejection fraction at baseline and during treatment.

Etoposide

ATC code: L01CB01

Capsule, 50 mg, LOU 5

Capsule, 100 mg, LOU 5

Injection, 20 mg/mL in 5 mL vial, LOU 5

Indications and dose

Adult

Stage 4 neuroblastoma, germ cell tumours, intracranial germ cell tumours, rhabdomyosarcoma, soft tissue sarcomas, neuroectodermal tumours (including medulloblastoma), relapsed Hodgkin disease, non-Hodgkin lymphoma, Ewing tumour, acute lymphoblastic leukaemia, acute myeloid leukaemia: Consult specialist protocols.

Paediatric: Consult specialist protocols.

Contraindications: Pregnancy, breastfeeding, severe hepatic impairment, allergy to polysorbate 80, etoposide, benzyl alcohol, intrathecal administration.

Precautions: Hepatic and renal impairment.

Renal impairment: Consider dose reduction. Mild impairment: 80–85% of normal dose.

Moderate to severe impairment: 50–75% of normal dose.

Hepatic impairment: Reduce dose according to serum bilirubin concentration.

- Do not use etoposide in severe hepatic impairment or if bilirubin > 85 micromol/L.
- Bilirubin 20–50 micromol/L: reduce dose by 50%.
- Bilirubin > 50 micromol/L: reduce dose by 75%.

Adverse effects: Common: Anorexia, constipation, abdominal pain, taste alteration, weakness, malaise, myelosuppression (see below), alopecia, nausea, vomiting, oral mucositis, diarrhoea, hypersensitivity reactions. Hypotension (with rapid infusion), peripheral neuropathy. Rare: Heart failure, cardiac arrest, radiation recall, dermatitis, SJS, secondary malignancies.

Myelosuppression: Major dose-limiting adverse effect. Mainly affects white cells but platelets and red cells are also affected. Neutrophil nadir occurs 7–14 days after administration. Recovery of bone marrow usually takes about 20 days.

Interactions with other medicines (*indicates serious):

- Ciclosporin: possibly increased plasma concentration of etoposide (increased risk of toxicity).
- Phenobarbital: possibly reduced plasma concentration of etoposide.
- Phenytoin: possibly reduced absorption of phenytoin and possibly reduced plasma concentration of etoposide.
- Vaccines, live: avoid use of live vaccines with etoposide (impairment of immune response).
- *Warfarin: possibly enhanced anticoagulant effect.

Notes:

- For oral therapy it may be necessary to give different doses on different days in order to administer dose within whole capsule units. Capsules should be swallowed whole on an empty stomach.
- Administration: Do not administer by rapid IV injection. Administer by continuous IV infusion or by IV intermittent infusion via an in-line 0.22 micron filter over at least 60 minutes at a rate not to exceed 100 mg/m2 per hour (or 3.3 mg/kg per hour) to minimize the risk of hypotensive reactions.

Fluorouracil (5-Fluorouracil or 5FU)

ATC code: L01BC02

Injection, 50 mg/mL (5-mL vial), LOU 5

Adult

Indications and dose

Treatment and palliation of solid tumours: Consult specialist protocols.

Paediatric: Consult specialist protocols.

Contraindications: Pregnancy, breastfeeding, dihydropyrimidine dehydrogenase deficiency.

Precautions: Pre-existing cardiac disease, hepatic impairment.

Renal impairment: Dose reduction not required.

Hepatic impairment: Severe: not recommended.

Adverse effects: Adverse effects differ depending on whether fluorouracil is given as a bolus dose or by continuous infusion. Myelotoxicity is common with bolus doses but unusual with continuous infusions. Palmar-plantar erythrodysaesthesia is common with continuous infusion. Common: Myelosuppression (see below), GI effects including nausea, vomiting, oral mucositis and diarrhoea (see below), alopecia, itch, maculopapular rash, ovarian failure, amenorrhoea. Oesophagitis, GI ulceration and bleeding, proctitis, palmar-plantar erythrodysaesthesia, photosensitivity, confusion, ataxia, nystagmus, headache, acute cerebellar syndrome, lacrimation, visual changes, photophobia. Rare: Myocardial ischaemia, arrhythmias, anaphylaxis and allergic reactions, fever without signs of infection, vein pigmentation.

Myelosuppression: Includes neutropenia, thrombocytopenia and anaemia. Neutropenic nadir occurs 9–14 days, but may be as late as 25 days, after first course. Platelet nadir occurs about 7–17 days after a dose, with recovery after about a further 10 days.

Diarrhoea: May be dose limiting and is more severe if given with calcium folinate. Consider fluid and electrolyte replacement.

Interactions with other medicines (*indicates serious):

- Metronidazole: metabolism of fluorouracil inhibited (increased toxicity).
- Phenytoin: metabolism of phenytoin possibly inhibited (increased risk of toxicity).
- Vaccines, live: avoid use of live vaccines with fluorouracil (impairment of immune response).
- *Warfarin: anticoagulant effect possibly enhanced.

Gemcitabine

ATC code: L01BC05

Powder for injection, 200-mg vial, LOU 5

Powder for injection, 1-g vial, LOU 5

Indications and dose

Adult

- *First-line treatment for locally advanced or metastatic non-small cell lung cancer (as monotherapy in elderly patients and in palliative treatment, otherwise in combination with cisplatin)*
- *Locally advanced or metastatic pancreatic cancer*
- *Advanced or metastatic bladder cancer (in combination with cisplatin)*
- *Locally advanced or metastatic epithelial ovarian cancer which has relapsed after a recurrence-free interval of at least 6 months following previous platinum-based therapy (in combination with carboplatin)*
- *Metastatic breast cancer which has relapsed after previous chemotherapy, including an anthracycline (in combination with paclitaxel)*

Adult: Consult local protocol.

Paediatric: No dosing recommendations available

Hepatic impairment: caution (limited information available).

Renal impairment: caution

Conception and contraception: effective contraception during treatment advised

Men must avoid fathering a child during and for 6 months after treatment.

Pregnancy: avoid (teratogenic in animal studies).

Breastfeeding: discontinue breastfeeding.

Adverse effects: Common or very common: Alopecia, anaemia, appetite decreased, asthenia, back pain, bone marrow depression, chills, constipation, cough, diarrhoea, drowsiness, dyspnoea, fever. haematuria, headache, hyperhidrosis, influenza like illness, insomnia, leucopenia, myalgia, nausea, neutropenia, oedema, oral disorders, proteinuria, rhinitis, skin reactions, thrombocytopenia, vomiting. Uncommon: Respiratory disorders. Rare or very rare: Capillary leak syndrome, hypotension, MI, posterior reversible encephalopathy syndrome. SCARs. skin ulcer. thrombocytosis. Frequency not known: Arrhythmias, colitis ischaemic, gangrene, haemolytic uraemic syndrome, heart failure, hepatic disorders, pulmonary oedema, radiation injuries, renal failure, stroke, vasculitis.

Gemcitabine should be discontinued if signs of microangiopathic haemolytic anaemia occur.

Interactions with other medicines:

Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.

Hydroxycarbamide (Hydroxyurea)

ATC code: L01XX05

Solid oral dose form 500 mg, LOU 5

Indications and dose

Adult

Polycythaemia vera (specialist use only), oral: Initially 15–20 mg/kg daily, adjusted according to response: for information on dose adjustment based on haematocrit and platelet count, consult product literature; usual dose 500–1000 mg daily; dosage should be based on actual or ideal body weight, whichever is less

Essential thrombocythaemia (specialist use only), oral: Initially 15 mg/kg daily, adjusted according to response; for information on dose adjustment based on platelet count and white cell count, consult product literature; dosage should be based on actual or ideal body weight, whichever is less

Chronic myeloid leukaemia (specialist use only), oral: Initially 40 mg/kg daily, then reduced to 20 mg/kg daily, adjusted according to response; for information on dose adjustment based on white cell count, consult product literature; dosage should be based on actual or ideal body weight, whichever is less

Cancer of the cervix (specialist use only), oral: 20–30 mg/kg daily, alternatively 80 mg/kg every 3 days; for information on dose adjustment based on platelet count, white cell count, and actual or ideal body weight, consult product literature

Sickle-cell disease (prevention of recurrent vaso-occlusive crises) (initiated by a specialist), oral: Initially 15 mg/kg daily, increased in steps of 2.5–5 mg/kg daily, dose to be increased every 12 weeks according to response; usual dose 15–30 mg/kg daily; maximum 35 mg/kg per day

Sickle-cell disease (prevention of vaso-occlusive complications) (specialist use only), oral: Initially 15 mg/kg daily, increased in steps of 5 mg/kg daily, dose to be increased every 8 weeks according to response; usual maintenance 20–25 mg/kg daily; maximum 35 mg/kg per day

Paediatric

Sickle-cell disease (prevention of recurrent vaso-occlusive crises) (initiated by a specialist), oral

Child 2–17 years: Initially 10–15 mg/kg once daily, increased in steps of 2.5–5 mg/kg daily, dose to be increased every 12 weeks according to response; usual dose 15–30 mg/kg daily; maximum 35 mg/kg per day

Sickle-cell disease (prevention of vaso-occlusive complications) (specialist use only), oral **Child 2–17 years:** Initially 15 mg/kg daily, increased in steps of 5 mg/kg daily, dose to be increased every 8 weeks according to response; usual maintenance 20–25 mg/kg daily; maximum 35 mg/kg per day

Precautions Leg ulcers (review treatment if cutaneous vasculitic ulcerations develop)

Hepatic impairment: manufacturer advises caution in mild to moderate impairment, avoid in severe impairment (unless used for malignant conditions).

Renal impairment in sickle-cell disease, avoid if eGFR less than 30 mL/min/1.73 m2. Use with caution in malignant disease. Dose adjustments in sickle-cell disease, reduce initial dose by 50% if egfr less than 60 mL/min/1.73 m2.

Conception and contraception: effective contraception before and during treatment advised

Pregnancy: avoid (teratogenic in animal studies).

Breastfeeding: discontinue breastfeeding.

Adverse effects: Common or very common: Alopecia, anaemia, appetite decreased, asthenia, bone marrow disorders, chills, constipation, cutaneous vasculitis, dermatomyositis, diarrhoea, disorientation, dizziness, drowsiness, dyspnoea, dysuria, fever. GI discomfort. haemorrhage, hallucination, headache, hepatic disorders, leucopenia, malaise, mucositis, nail discolouration, nail disorder. nausea, neoplasms, neutropenia, oral disorders, pancreatitis, peripheral neuropathy, pulmonary oedema. red blood cell abnormalities. respiratory disorders, seizure, skin reactions, skin ulcers, sperm abnormalities, thrombocytopenia, vomiting. Rare or very rare: Cutaneous lupus erythematosus, gangrene, SLE. Frequency not known: Amenorrhoea, GI disorders, hypomagnesaemia, Parvovirus B19 infection, vitamin D deficiency, weight increased

Interactions with other medicines:

» Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.

» Increased risk of toxicity with stavudine.

Notes

» Monitoring requirements: monitor renal and hepatic function before and during treatment.

» Monitor full blood count before treatment, and repeatedly throughout use, in sickle-cell disease monitor every 2 weeks for the first 2 months and then every 2 to 3 months thereafter (or every 2 weeks if on maximum dose).

» Patients receiving long-term therapy for malignant disease should be monitored for secondary malignancies.

» Patient and Caregiver advice: patients receiving long-term therapy with hydroxycarbamide should be advised to protect skin from sun exposure.

Ifosfamide + Mesna

ATC code: L01AA06, V03AF01

Injection, 1 g + 600 mg, LOU 5

Injection, 2 g + 1200 mg, LOU 5

Indications and dose

Adult

Malignant disease rhabdomyosarcoma, soft-tissue sarcomas, Ewing tumour, germ cell tumour, osteogenic sarcoma, by IV infusion: Consult local protocol.

Paediatric

Rhabdomyosarcoma, soft-tissue sarcomas, Ewing tumour, germ cell tumour, osteogenic sarcoma, by IV infusion

Child: Consult local protocol.

Contraindications: Acute infection, cystitis, urinary tract obstruction, urothelial damage

Precautions: Avoid in Acute porphyrias. diabetes mellitus

Hepatic impairment: avoid.

Renal impairment: avoid if serum creatinine concentration greater than 120 micromol/L.

Conception and contraception: adequate contraception advised during and for at least 6 months after treatment in men or women.

Pregnancy: avoid (teratogenic and carcinogenic in animals).

Breastfeeding: discontinue breastfeeding.

Adverse effects: Common or very common: Alopecia, appetite decreased, bone marrow disorders, haemorrhage, hepatic disorders, infection, leucopenia, nausea, reactivation of infection, renal impairment, thrombocytopenia, vomiting. Uncommon: Cardiotoxicity, diarrhoea, hypotension, oral disorders. Rare: Skin reactions. Frequency not known: Abdominal pain, agranulocytosis, amenorrhoea, anaemia, angina pectoris, angioedema, arrhythmias, arthralgia, asterixis, behaviour abnormal, blood disorders, bone disorders, cancer progression, capillary leak syndrome, cardiac arrest. cardiomyopathy, chills, conjunctivitis, constipation, cough, deafness, delirium, delusions, disseminated intravascular coagulation, dysarthria, dyspnoea, electrolyte imbalance, embolism and thrombosis, encephalopathy, eye irritation, fatigue, fever. flushing, gait abnormal, GI disorders, growth retardation, haemolytic anaemia, heart failure, hyperglycaemia, hyperhidrosis, hyperphosphaturia, hypertension, hypoxia, immunosuppression, infertility, malaise, mania, memory loss, metabolic acidosis, movement disorders, mucosal ulceration, multi organ failure, muscle complaints, MI, nail disorder. neoplasms, nephritis tubulointerstitial, nephrogenic diabetes insipidus, neurotoxicity, oedema, ovarian and fallopian tube disorders, pain, pancreatitis, panic attack, peripheral neuropathy, polydipsia, premature menopause, psychiatric disorders, pulmonary hypertension, pulmonary oedema. radiation recall reaction. respiratory disorders. rhabdomyolysis, secondary malignancy, sensation abnormal, sepsis, SCARs. SIADH, sinusoidal obstruction syndrome, sperm abnormalities, status epilepticus, tinnitus. tumour lysis syndrome, urinary disorders, vasculitis, vertigo, visual impairment

Interactions with other medicines → alkylating agents

» Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, carboplatin, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.

» Increased risk of nephrotoxicity on concurrent use with other nephrotoxic agents including: Aceclofenac, acyclovir, amikacin, amphotericin, bacitracin, capreomycin, carboplatin, cephalexin, cefixime, ceftazidime, ciclosporin, cisplatin, dexketoprofen, diclofenac, etoricoxib, ganciclovir, ibuprofen, gentamicin, ketoprofen, mefenamic acid, indomethacin, meloxicam, methotrexate, oxaliplatin, piroxicam, streptomycin, tacrolimus, trimethoprim, vancomycin, tenofovir disoproxil, zidovudine, zoledronate.

Notes

- Urothelial toxicity: Mesna is routinely given with ifosfamide to reduce urothelial toxicity. Secondary malignancy: Use of ifosfamide is associated with an increased incidence of acute leukaemia.
- Monitoring requirements: ensure satisfactory electrolyte balance and renal function before each course (risk of tubular dysfunction, fanconi's syndrome or diabetes insipidus if renal toxicity not treated promptly).

Irinotecan

ATC code L01CE02

Injection, 20 mg/mL (2-mL vial), LOU 5

Injection, 20 mg/mL (5-mL vial), LOU 5

Indications and dose

Adult

- *Metastatic colorectal cancer in combination with fluorouracil and folinic acid or as monotherapy when treatment containing fluorouracil has failed*
- *Epidermal growth factor receptor-expressing metastatic colorectal cancer after failure of chemotherapy that has included irinotecan (in combination with cetuximab)*
- *First-line treatment of metastatic carcinoma of the colon or rectum (in combination with fluorouracil, folinic acid and bevacizumab)*
- *First-line treatment of metastatic colorectal carcinoma (in combination with capecitabine with or without bevacizumab)*

Adult dose: Consult product literature or local protocols.

Metastatic adenocarcinoma of the pancreas in patients who have progressed following gemcitabine-based therapy (in combination with fluorouracil and leucovorin) (specialist use only), by IV infusion using lipid formulation: Consult product literature or local protocols.

Paediatric: No or insufficient experience in children and adolescents therefore its use is not recommended.

Contraindications: Bowel obstruction. chronic inflammatory bowel disease

Precautions: Raised plasma-bilirubin concentration, risk factors for cardiac disease, risk factors for pulmonary toxicity, underweight patients—increased risk of adverse events

Adverse effects: Common or very common: Alopecia, anaemia (dose limiting). appetite decreased, asthenia, cholinergic syndrome, constipation, decreased leucocytes, diarrhoea (delayed diarrhoea requires prompt treatment), dizziness, dysphonia, dyspnoea, electrolyte imbalance, embolism and thrombosis, febrile neutropenia (dose-limiting), fever, fluid imbalance, GI discomfort, GI disorders, hypoalbuminaemia, hypoglycaemia, hypotension, increased risk of infection, infusion related reaction, insomnia, mucositis, nausea, neutropenia (dose-limiting), oedema, renal impairment, sepsis, stomatitis, taste altered, thrombocytopenia (dose limiting), vomiting, weight decreased. Uncommon: Hypersensitivity, hypoxia, nail discolouration, skin reactions. Frequency not known: Antibiotic associated colitis, circulatory collapse, GI haemorrhage, hiccups, hypertension, interstitial lung disease, muscle cramps, paraesthesia, speech disorder. ulcerative colitis

Interactions with other medicines:

- Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, cisplatin, chlorambucil, cyclophosphamide, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, carboplatin, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.
- Drugs that increase concentration of irinotecan: Antifungals: ketoconazole, fluconazole. Macrolides. Avoid or adjust dose. Protease inhibitors
- Drugs that decrease concentration of irinotecan: Antiepileptics (phenobarbitone, carbamazepine, phenytoin). Rifampicin. St John's wort
- Increased risk of prolonged neuromuscular blockade with suxamethonium Increased risk of thrombotic events with: Tranexamic acid, bleomycin, cyclophosphamide, doxorubicin, fluorouracil, methotrexate, tamoxifen, vincristine.

Notes:

- Irinotecan inhibits topoisomerase I, an enzyme involved in DNA replication
- Irinotecan has been associated with reports of serious thromboembolic events, such as pulmonary embolism, venous thrombosis, and arterial thromboembolism.
- Health care professionals are advised to obtain a thorough medical history to identify patients with multiple risk factors.
- Patients should be advised to seek medical advice immediately if signs or symptoms of thromboembolism occur, such as sudden pain and swelling in a leg or an arm, sudden onset of coughing, chest pain or difficulty breathing.

L-Asparaginase

ATC code: L01XX02

Powder for injection, 10 000 IU in vial, LOU 5

Indications and dose

Adult

Acute lymphoblastic leukaemia, T-cell non-Hodgkin lymphoma: See specialist treatment protocols.

Paediatric: See specialist treatment protocols.

Contraindications: Allergy to asparaginase, history of pancreatitis, history of thrombosis or haemorrhagic

events with previous asparaginase therapy, pregnancy.

Precautions: Underlying coagulopathy, impaired renal function, pre-existing liver impairment, discontinue at the first sign of renal failure or pancreatitis, appropriate measures should be taken to prevent hyperuricaemia and uric acid nephropathy (consider allopurinol, hydration and urinary alkalinization), test dose recommended: An intradermal test dose of 2 units is often recommended prior to the first dose of asparaginase or prior to restarting therapy after a hiatus of several days. However, false negative rates of up to 80% are reported. Serious allergic reactions can occur, intradermal testing should only be done in a hospital setting with adequate monitoring and resuscitation facilities. Desensitization may be performed in patients who are found to be hypersensitive from the intradermal test dose, consult specialist texts for details.

Renal impairment: Use with caution.

Hepatic impairment: Use with caution.

Adverse effects: Children appear to tolerate asparaginase better than adults. Common: Allergic reactions, nausea, vomiting, fatty changes in the liver, elevated transaminases and bilirubin, decreased albumin and calcium concentrations, reduced fibrinogen and clotting factors (resulting in prolonged clotting times), uraemia, pancreatitis. Transient proteinuria, hyperglycaemia (rarely leading to diabetic ketoacidosis), CNS effects including depression or hyperexcitability, chills and fever (possibly caused by bacterial endotoxins in the preparation), increased fibrin degradation products, increased blood ammonia. Rare: Intracranial haemorrhage or thrombosis, peripheral venous and arterial thrombosis, transient myelosuppression, acute renal failure, Parkinsonian-like syndrome, diarrhoea, oral mucositis.

Interactions with other medicines (*indicates serious):

- Vaccines, live: avoid use of live vaccines with asparaginase (impairment of immune response).
- Cytarabine: decreased antineoplastic effect if given prior to cytarabine.
- Methotrexate: decreased antineoplastic effect if given prior to methotrexate.
- Prednisolone: increased hyperglycaemic effect.

Notes:

- Can be produced by either *Erwinia chrysanthemi* or *Escherichia coli.* Children who are hypersensitive to asparaginase derived from one organism may tolerate asparaginase derived from another organism but cross-sensitivity occurs in 20–30% of individuals.
- Asparaginase is a contact irritant. Care should be taken to avoid contact with skin or mucous membranes (especially eyes). If accidental contact occurs, the affected area should be flushed with water for at least 15 minutes.
- Different brands of asparaginase may not be interchangeable and the units may be expressed differently.
- Allergic reactions to asparaginase are frequent and can be fatal. Risk factors include IV administration, large doses, prior exposure to asparaginase and intervals of even a few days between doses. An intradermal test dose may be administered (see Precautions)

Liposomal Doxorubicin

ATC code L01DB01

Solution for injection (Pegylated), 20 mg, 50 mg vial, LOU 5

Indications and dose

Adult

AIDS-related Kaposi's sarcoma, by IV: 20 mg/m2/dose once every 3 weeks

Breast cancer, by IV: 20–80 mg/m2/dose every 8 weeks

Ovarian cancer, by IV: 50 mg/m2/dose every 4 weeks

Solid tumors, by IV: 50–60 mg/m2/dose every 3–4 weeks

Paediatric: Consult specialist protocols.

Contraindications: Hypersensitivity to doxorubicin, other anthracyclines, or any component of the formulation, breastfeeding, pregnancy

Precautions: In patient with high cumulative doses of anthracyclines, anthracenediones, and cyclophosphamide, patients with previous thoracic radiation or who have pre-existing cardiac disease

Adverse effects: Peripheral edema, fever, headache, pain, alopecia, palmar-plantar, erythrodysesthesia/ hand-foot syndrome, rash, 11. Antineoplastic And Adjuvants 650 stomatitis, vomiting, nausea, constipation, anorexia, neutropenia, leucopenia, cytopenia, anemia, weakness, agitation, confusion, acne, dry skin

Interactions with other medicines: Cylosporine, allopurinol, cyclophosphamide, mercaptopurine, streptozocin, verapamil, paclitaxel, progesterone, bupropion, promethazine, propofol, selegiline, sertraline, and other CYP2B6 substrates, azole antifungals, chlorpromazine, clarithromycin, diclofenac, doxycycline, erythromycin, isoniazid, quinine, ritonavir, aminoglutethimide, carbamazepine, nafcillin, nevirapine, Phenobarbital, phenytoin, rifamycins and other CYP3A4 inducers, digoxin, zidovudine, live vaccines.

Melphalan

ATC code L01AA03

Tablet, 2 mg, LOU 5

Powder for injection, 50-mg vial, LOU 5

Indications and dose

Adult

Multiple myeloma, oral: 150 micrograms/kg daily for 4 days; dose to be repeated every 6 weeks; dose may vary according to regimen

Multiple myeloma, by IV injection or IV infusion: Consult product literature.

Polycythaemia vera, oral: Initially 6–10 mg daily for 5–7 days, then reduced to 2–4 mg daily until satisfactory response, then reduced to 2–6 mg once weekly

Localised malignant melanoma of the extremities,

localised soft-tissue sarcoma of the extremities, by regional arterial perfusion: Consult local protocol.

Paediatric

High IV dose with haematopoietic stem cell transplantation to treat childhood neuroblastoma and some other advanced embryonal tumours, by IV infusion

Child: Consult local protocol.

Renal impairment dose adjustments: reduce dose initially

Conception and contraception: adequate contraception advised during treatment in men or women.

Pregnancy: avoid.

Breastfeeding: discontinue breastfeeding.

Adverse effects: Common or very common: Alopecia, anaemia, bone marrow depression (delayed). diarrhoea, nausea, stomatitis, thrombocytopenia, vomiting. Specific with oral use: Leucopenia. Specific with parenteral use: Feeling hot. myalgia, myopathy, paraesthesia. Rare or very rare: Haemolytic anaemia, hepatic disorders, respiratory disorders, skin reactions. Specific with parenteral use: Peripheral vascular disease

Secondary malignancy: Use of melphalan is associated with an increased incidence of acute leukaemias

Interactions with other medicines ⍰ alkylating agents

- Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, carboplatin, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.
- Increased risk of nephrotoxicity on concurrent use with other nephrotoxic agents including: Aceclofena, acyclovir, amikacin, amphotericin, bacitracin, capreomycin, carboplatin, cephalexin, cefixime, ceftazidime, ciclosporin, cisplatin, dexketoprofen, diclofenac, etoricoxib, ganciclovir, gentamicin, ibuprofen, gentamicin, ketoprofen, mefenamic acid, indomethacin, meloxicam, methotrexate, oxaliplatin, piroxicam, streptomycin, tacrolimus, trimethoprim, vancomycin, tenofovir disoproxil, zidovudine, zoledronate.

Notes: Monitoring requirements: monitor full blood count before and throughout treatment.

Mercaptopurine

ATC code L01BB02

Tablet, 50 mg, LOU 5

Indications and dose

Adult

Acute leukaemias, chronic myeloid leukaemia, oral: Initially 2.5 mg/kg daily, adjusted according to response; alternatively, initially 50–75 mg/m2 daily, adjusted according to response. Reduce dose to one-quarter of the usual dose with concurrent use of allopurinol.

Paediatric

Acute lymphoblastic leukaemia, lymphoblastic lymphomas, oral

Child: Consult local protocol.

Dose adjustments due to interactions: Reduce dose to one-quarter of the usual dose with concurrent use of allopurinol.

Contraindications: Absent thiopurine methyltransferase activity

Precautions: Reduced thiopurine methyltransferase activity. The enzyme thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine, tioguanine), the risk of myelosuppression is increased in patients with reduced activity of the enzyme, particularly for the few individuals in whom TPMT activity is undetectable. Patients with absent TPMT activity should not receive thiopurine drugs, those with reduced TPMT activity may be treated under specialist supervision.

Hepatic impairment: consider dose reduction

Renal impairment dose adjustments: reduce dose.

Conception and contraception: contraceptive advice required.

Pregnancy: avoid (teratogenic).

Breastfeeding: discontinue breastfeeding.

Adverse effects: Common or very common: Anaemia, appetite decreased, bone marrow depression, diarrhoea, hepatic disorders, hepatotoxicity (more common at high doses), leucopenia, nausea, oral disorders, pancreatitis, thrombocytopenia, vomiting. Uncommon: Arthralgia, fever, increased risk of infection, neutropenia, rash. Rare or very rare: Alopecia, face oedema, intestinal ulcer. neoplasms, oligozoospermia. Frequency not known: Photosensitivity reaction

Interactions with other medicines:

- Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, carboplatin, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.

» Increased risk of hepatotoxicity on concurrent use with other hepatotoxic agents including: Atorvastatin, bedaquiline, carbamazepine, clavulanate, doxycycline, flucloxacillin, fluconazole, isoniazid, leflunomide, methotrexate, paracetamol, tetracycline, valproate, sulfasalazine.

Notes

» Dose equivalence and conversion: Mercaptopurine tablets and oral suspension are not bioequivalent. Haematological monitoring is advised when switching formulations.

» Not licensed for use in severe ulcerative colitis and Crohn's disease.

» Mercaptopurine has been confused with mercaptamine, care must be taken to ensure the correct drug is prescribed and dispensed.

» Pre-treatment screening: consider measuring thiopurine methyltransferase activity before starting mercaptopurine therapy. Monitoring requirements: monitor liver function.

Methotrexate

ATC code: L04AX03

Injection, 25 mg (as sodium salt)/mL (2-mL vial) preservative free, LOU 5

Injection, 25 mg (as sodium salt)/mL (20-mL vial), LOU 5

Tablet, 2.5 mg, 10 mg (as sodium salt), LOU 5

Indications and dose

Adult

Maintenance and remission of acute lymphoblastic leukaemia, lymphoblastic lymphoma, treatment of early stage Burkitt lymphoma, non-Hodgkin lymphoma, osteogenic sarcoma, some neurological tumours, including infant brain tumours, meningeal leukaemia, treatment and prevention of neurological involvement of leukaemia: High-dose methotrexate requires specialist supportive care, such as alkalinization of the urine and calcium folinate rescue; consult specialist protocols.

Paediatric: Consult specialist protocols

Contraindications: Pregnancy, breastfeeding, severe renal impairment, severe hepatic impairment.

Precautions: Monitor renal and hepatic function, peptic ulceration, ulcerative colitis, diarrhoea, ulcerative stomatitis, porphyria, pre-existing bone marrow suppression, concurrent use of other hepatotoxic drugs.

Renal impairment: Accumulates, nephrotoxic.

» Mild: 50–100% of normal dose.

» Moderate: 50% of normal dose.

» Severe: contraindicated. Or refer to instructions in specialist protocols.

Hepatic impairment: Dose-related toxicity: avoid in severe hepatic impairment.

Adverse effects: Common: Myelosuppression (see below), nausea and vomiting (more frequent with high doses), oral mucositis, pulmonary toxicity (see below), hepatotoxicity (see below), rash, itch, urticaria, photosensitivity, neurotoxicity (e.g., aseptic meningitis, encephalopathy, leukoencephalopathy) with high-dose or intrathecal use. Uncommon: Malaise, fatigue, chills, fever, headache, dizziness, tinnitus, blurred vision, alopecia, ocular irritation, oligospermia (transient). Rare: Anaphylactic/anaphylactoid reactions, severe skin reactions (e.g., SJS, toxic epidermal necrolysis), nephrotoxicity including renal failure, osteoporosis, skin and bone necrosis, macrocytic anaemia.

Myelosuppression: Includes neutropenia, thrombocytopenia and anaemia. Neutrophil and platelet nadirs occur about 5–13 days after a bolus dose with recovery between 14 and 28 days. Neutropenia may sometimes be biphasic with the first nadir 4–7 days after a dose and the second at 12–21 days. Pancytopenia may occur and is potentially fatal.

Hepatotoxicity: Increased aminotransferases are common and usually transient and asymptomatic. Chronic hepatotoxicity (including necrosis, fatty change, periportal fibrosis or cirrhosis) generally occurs with long-term therapy and is also dependent on cumulative dose.

Pulmonary toxicity: Can develop rapidly and may be fatal. Often occurs as fever, dyspnoea, chest pain and dry, non-productive cough. Lesions such as pneumonitis and pulmonary fibrosis can occur at all doses at any time during treatment. Pulmonary toxicity may not be fully reversible, corticosteroids may relieve symptoms. Also consider the possibility of infection.

Interactions with other medicines (*indicates serious):

» *Acetylsalicylic acid: reduced excretion of methotrexate (increased toxicity).

» Amoxicillin: reduced excretion of methotrexate (increased risk of toxicity).

» Ampicillin: reduced excretion of methotrexate (increased risk of toxicity).

» Benzylpenicillin: reduced excretion of methotrexate (increased risk of toxicity).

» *Ciclosporin: increased toxicity.

» *Cisplatin: risk of toxicity, particularly pulmonary.

» *Dexamethasone: increased risk of haematological toxicity.

» Doxycycline: increased risk of methotrexate toxicity.

» *Hydrocortisone: increased risk of haematological toxicity.

» *Ibuprofen: excretion of methotrexate reduced (increased risk of toxicity).

» *Nitrous oxide: increased antifolate effect (avoid concomitant use).

» Omeprazole: increased risk of methotrexate toxicity.

» Phenoxymethylpenicillin: reduced excretion of methotrexate (increased risk of toxicity).

» Phenytoin: reduced absorption of phenytoin, antifolate effect of methotrexate increased.

» *Prednisolone: increased risk of haematological toxicity.

- *Pyrimethamine: antifolate effect of methotrexate increased
- Silver sulfadiazine: increased risk of methotrexate toxicity.
- Sulfadiazine: risk of methotrexate toxicity increased.
- *Sulfadoxine + pyrimethamine: antifolate effect of methotrexate increased, risk of methotrexate toxicity increased.
- *Sulfamethoxazole + trimethoprim: antifolate effect of methotrexate increased (avoid concomitant use), risk of methotrexate toxicity increased.
- *Trimethoprim: antifolate effect of methotrexate increased (avoid concomitant use).
- Vaccines, live: avoid use of live vaccines with methotrexate (impairment of immune response).
- *Warfarin: increased risk for elevated INR and subsequent bleeding.

Notes:

- High-dose methotrexate may cause precipitation of methotrexate or its metabolites in renal tubules. A high fluid throughput and alkalinization of urine, using sodium hydrogen carbonate if necessary, is recommended.
- Patients or their caregivers should be advised to report any feature of blood disorders (e.g., sore throat, bruising and mouth ulcers), liver toxicity (e.g., nausea, vomiting, abdominal discomfort and dark urine) and respiratory toxicity (e.g., dry cough, shortness of breath).
- Advise patients to avoid sunlight, wear protective clothing, wide-brimmed hats, sunglasses and lip sunscreen.
- Calcium folinate rescue is required for high-dose methotrexate doses, refer to specialist protocols.

Mitomycin C

ATC code: L01DC03

PFI, 10mg, (vial), LOU5

Indications and dose

Adult

Anal carcinoma:

Intravascular injection: 10 mg/m2 (max 20mg) as a bolus on days 1 and 29 in combination with fluorouracil and radiation therapy. Or 12 mg/m2 (max 20mg) on day 1 only in combination with fluorouracil and radiation. Or 12 mg/m2 (max 20mg) on day 1 only in combination with capecitabine and radiation.

Non muscle invasive bladder cancer (intravesicular):

Intravesicular instillation: 40 mg instilled into the bladder once weekly or 2 weekly or monthly or 3 monthly for 1-2 hours duration of therapy should be on an individual patient basis.

Muscle invasive bladder cancer:

Intravascular injection: 12 mg/m2 (max 20mg) as a bolus on days 1 only in combination with fluorouracil and radiation therapy.

Dosage modifications for toxicity:

- Leukocytes 3000<4000/mm3, or platelets 75,000 to < 100,000/mm3 hold therapy until leukocyte count≥4000/mm3 and platelets ≥ 100,00/mm3 then resume 100% of prior dose in subsequent cycles.
- Leukocytes 2000 to<3000/mm3 or platelets 25000 to < 75,000/mm3 hold therapy until leukocyte count≥4000/mm/3 and platelets ≥ 100,00/mm3 then reduce dose to 70% of prior dose in subsequent cycles.
- Leukocytes <2000/mm3 or platelets < 25,000/mm3 hold therapy until leukocyte count≥4000/mm/3 and platelets ≥ 100,00/mm3 then reduce dose to 50% of prior dose in subsequent cycles.

Paediatric

Safety and efficacy in children has not been established.

Contraindications: Hypersensitivity to the active substance or any of the excipients, breastfeeding, bladder wall perforation, cystitis, thrombocytopenia.

Precautions:

- Extravasation: Is a potent vesicant ensure proper needle or catheter placement prior to and during infusion to avoid extravasation.
- Haemolytic uremic syndrome: consisting of microangiopathic haemolytic anaemia, thrombocytopenia and irreversible renal failure may occur, mainly at doses greater than or equal to 60mg .
- Bone marrow suppression: mainly thrombocytopenia and leukopenia which can lead to life threatening infections.
- Pulmonary toxicity: acute respiratory distress syndrome has been reported in patients receiving therapy in combination with other chemotherapy.

Hepatic impairment: Mild to moderate Impairment: No dose adjustment is necessary. Severe impairment: Consider reducing dose to 50% of original dose.

Renal impairment:

Creatinine clearance: >10 ml/min: Dose as in normal renal function.

Creatinine clearance :<10 ml/min: 75% of normal dose.

Pregnancy: Use not recommended in pregnancy. Women of childbearing age should use effective contraception during treatment and for 6 months following the last dose. Males with female partners should use effective contraception during treatment and for 3 months following the last dose.

Breastfeeding: Use not recommended during breastfeeding and patients should not breastfeed during treatment and for 1 week following the last dose.

Adverse effects: Myelosuppression, haemolytic uremic syndrome, nausea/vomiting, stomatitis, Increased serum creatinine, mucous membrane toxicity, pulmonary toxicity, hepatic sinusoidal obstruction syndrome, irreversible renal failure, fever.

Interactions with other medicines (*indicates serious): *Vinca alkaloids, bacitracin, *deferiprone, erdafitinib, lasmiditan, *palifermin, ropeginterferon alfa 2b, sotorasib and tepotinib,

Notes:

- Intravesical administration: Mitomycin 40 mg is introduced into the bladder using a catheter at low pressure. Patients should be mobilised or turned every 15 to 30 minutes to ensure sufficient contact with the entire mucosal surface. Should be retained for 1-2 hours after. Patient should void the instilled solution preferably in a sitting position.
- Extravasation during IV administration: If extravasation occurs stop infusion and disconnect cannula/needle, gently aspirate the extravasated solution and elevate extremity. DO NOT flush the line. Initiate dimethyl sulphate (DMSO) antidote and apply dry cold compress for 20 minutes 4 times per day for 1-2 days.

Oxaliplatin

ATC code L01XA03

Solution for injection, 2 mg/mL (25-mL vial), LOU 5

Solution for injection, 2 mg/mL (50-mL vial), LOU 5

Indications and dose

Adult

Metastatic colorectal cancer (in combination with fluorouracil and folinic acid), Colon cancer after resection of the primary tumour (adjuvant treatment), by IV infusion: Consult product literature.

Paediatric: No or insufficient experience in children and adolescents therefore its use is not recommended.

Contraindications: Peripheral neuropathy with functional impairment

Renal impairment: avoid if CrCl less than 30 mL/min, reduce dose in mild to moderate impairment

Pregnancy: avoid—toxicity in animal studies.

Breastfeeding: discontinue breastfeeding.

Adverse effects: Common or very common: Alopecia, anaemia, appetite decreased, arthralgia, asthenia, chills, conjunctivitis, constipation, cough, decreased leucocytes, dehydration, depression, diarrhoea, dizziness, dyspnoea, electrolyte imbalance, embolism and thrombosis, fever, flushing, GI discomfort, GI disorders, haemorrhage, headache, hiccups, hyperglycaemia, hyperhidrosis, hypersensitivity, hypertension, increased risk of infection, insomnia, meningism, mucositis, nail disorder, nausea, necrosis, nerve disorders, neutropenia, neutropenic sepsis, pain, peripheral neuropathy (dose-limiting), sensation abnormal, skin reactions, stomatitis, taste altered, thrombocytopenia, urinary disorders, vision disorders, vomiting, weight changes. Uncommon: Metabolic acidosis, nervousness, ototoxicity. Rare or very rare: Acute kidney injury, acute tubular necrosis, antibiotic associated colitis, deafness, disseminated intravascular coagulation, dysarthria, haemolytic anaemia, hepatic disorders, immuno-allergic thrombocytopenia, nephritis acute interstitial, nodular regenerative hyperplasia, pancreatitis, posterior reversible encephalopathy syndrome (with oxaliplatin combination chemotherapy), respiratory disorders, sinusoidal obstruction syndrome, vision loss (reversible on discontinuation). Frequency not known: Autoimmune pancytopenia, chest discomfort, dysphagia, extravasation necrosis, gait abnormal, hypersensitivity vasculitis, movement disorders, muscle complaints, muscle contractions involuntary, QT interval prolongation, rhabdomyolysis, throat complaints.

Neurotoxicity is dose limiting.

Respiratory symptoms: If unexplained respiratory symptoms occur, oxaliplatin should be discontinued until investigations exclude interstitial lung disease and pulmonary fibrosis.

Interactions with other medicines: platinum compounds

- Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, carboplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.
- Increased risk of nephrotoxicity on concurrent use with other nephrotoxic agents including: Aceclofenac, acyclovir, amikacin, amphotericin, bacitracin, capreomycin, carboplatin, cephalexin, cefixime, ceftazidime, ciclosporin, cisplatin, dexketoprofen, diclofenac, etoricoxib, ganciclovir, gentamicin, ibuprofen, gentamicin, ketoprofen, mefenamic acid, indomethacin, meloxicam, methotrexate, piroxicam, streptomycin, tacrolimus, trimethoprim, vancomycin, tenofovir disoproxil, zidovudine, zoledronate.
- Increased risk of ototoxicity on concurrent use with other ototoxic agents including: Amikacin, cisplatin, furosemide, gentamicin, carboplatin, torsemide, vincristine, vinblastine, vancomycin.
- Increased risk of peripheral neuropathy on concurrent use with other agents causing it, including: Cisplatin, docetaxel, isoniazid, lamivudine, metronidazole, nitrofurantoin, paclitaxel, phenytoin, stavudine, vincristine, vinblastine, thalidomide.

Notes: Effective contraception required during and for 4 months after treatment in women and 6 months after treatment in men.

Paclitaxel

ATC code: L01CD01

Concentrate (for IV infusion)

6 mg/mL (5-mL vial) LOU 5

6 mg/mL (16.7-mL vial) LOU 5

6 mg/mL (50-mL vial) LOU 5

Indications and dose

Adult

Use in treatment of epithelial ovarian cancer, early stage and metastatic breast cancers, Kaposi sarcoma, nasopharyngeal cancer, non-small cell lung cancer, ovarian germ cell tumour; requires special (non-PVC) tubing (infusion set) because it absorbs through plastic

First-line treatment of ovarian cancer, by IV infusion: Depending on the duration of infusion, two different dosages may be used: paclitaxel 175 mg/m2 administered as an IV infusion over a period of three hours followed by 75 mg/m2 of cisplatin and the therapy is repeated at 3-week intervals, or paclitaxel 135 mg/m2 administered as an IV infusion over a period of 24 hours followed by 75 mg/m2 of cisplatin, and the therapy is repeated at 3-week intervals

Second-line treatment of ovarian cancer, by IV infusion: 175 mg/m2 administered over 3 hours, with a 3-week interval between courses

Adjuvant chemotherapy in breast carcinoma, by IV infusion: 175 mg/m2 administered over a period of 3 hours every 3 weeks for four courses, following AC therapy

First-line chemotherapy of breast carcinoma, by IV infusion:

- When used in combination with doxorubicin (50 mg/m2), paclitaxel should be administered 24 hours after doxorubicin. A dose of paclitaxel is 220 mg/m2 administered intravenously over a period of 3 hours, with a 3-week interval between courses.
- When used in combination with trastuzumab, a dose of paclitaxel 175 mg/m2 is administered intravenously over a period of 3 hours, with a 3-week interval between courses. Paclitaxel infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated.

Second-line chemotherapy of breast carcinoma, by IV infusion: 175 mg/m2 is administered over a period of 3 hours, with a 3-week interval between courses

Advanced non-small cell lung cancer, by IV infusion: 175 mg/m2 is administered over 3 hours followed by 80 mg/m2 of cisplatin, with a 3-week interval between courses

AIDS-related KS, by IV infusion: 100 mg/m² administered as a 3-hour IV infusion every two weeks

Dose adjustment: Subsequent doses of paclitaxel should be administered according to individual patient tolerance. Paclitaxel should not be readministered until the neutrophil count is ≥1.5 × 109/L (≥1 × 109/L for KS patients) and the platelet count is ≥100 × 109/L (≥75 × 109/L for KS patients).

Patients who experience severe neutropenia (neutrophil count <0.5 × 109/L for a minimum of 7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients).

Paediatric: Not recommended for use in children below 18 years because of the lack of data on safety and efficacy.

Contraindications: Severe hypersensitivity reactions to paclitaxel, macrogolglycerol ricinoleate (polyoxyl castor oil) or to any of the excipients. Paclitaxel is contraindicated during breastfeeding. Paclitaxel should not be used in patients with baseline neutrophils <1.5 x 109/L (<1 x 109/L for KS patients) or platelets <100 x 109/L (<75 x 109/L for KS patients). In KS, paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections. Patients with severe hepatic impairment must not be treated with paclitaxel.

Precautions: Female and male patients of reproductive age must take contraceptive measures for themselves and/or their sexual partners during and for at least 6 months after therapy. Male patients are advised to seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with paclitaxel. There have been reports of reduced visual acuity due to cystoid macular oedema (CME) during treatment with paclitaxel. Discontinue paclitaxel treatment if a CME diagnosis is confirmed.

Hepatic impairment: Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments. Patients with severe hepatic impairment must not be treated with paclitaxel.

Pregnancy: Paclitaxel may cause foetal harm when administered to pregnant women.

Breastfeeding: Breastfeeding should be discontinued for the duration of therapy with paclitaxel

Adverse effects: Bone marrow suppression, neurotoxicity, peripheral neuropathy, myalgia or arthralgia, CME, injection site reactions, Disseminated intravascular coagulation, alopecia

Interaction with other medicinal products and other forms of interaction

- *Cisplatin:* Paclitaxel is recommended to be administered *before* cisplatin. Administration of paclitaxel *after* cisplatin treatment leads to greater myelosuppression and about a 20% decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.
- *Doxorubicin:* Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin
- Sequence effects characterised by more

profound neutropenic and stomatitis episodes have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered before doxorubicin and using longer than recommended infusion times (paclitaxel administered over 24 hours, doxorubicin over 48 hours).

» *Active substances metabolised in the liver:* The metabolism of paclitaxel is catalysed, in part, by CYP 450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a PK drug-drug interaction study, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

Notes:

» The concentrate for solution for infusion must be diluted before use and should only be administered intravenously.

» Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.

» Patients must be pretreated with corticosteroids, antihistamines and H2 antagonists.

» Paclitaxel should be given before cisplatin when used in combination.

» When paclitaxel is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function.

Pegaspargase

ATC code: L01XX24

Injection, 3750 mg/5mL (5-mL vial), LOU 5

Indications and dose

Adult

Acute lymphoblastic leukaemia: Adults ≤ 21 years of age

Intravenous infusion/intramuscular injection: 2500 units/m2 every 14 days.

Acute lymphoblastic leukaemia: Adults> 21 years of age:

Intravenous infusion/intramuscular injection, 2000 units/m2 every 14 days.

Paediatric

Acute lymphoblastic leukaemia

Patients with a body surface area (BSA) ≥0.6 m2; intravenous infusion/intramuscular injection, 2500 units/m2 every 14 days

Patients with a body surface area (BSA) <0.6 m2 , intravenous infusion/intramuscular injection 82.5 units/kg every 14 days

Contraindications:

» Hypersensitivity to the active substance or to any of the excipients, Severe hepatic impairment (bilirubin >3 times upper limit of normal [ULN]; transaminases >10 times ULN),history of serious thrombosis with prior L-asparaginase therapy, history of pancreatitis, history of serious haemorrhagic events with prior L-asparaginase therapy.

Precautions:

» Hypersensitivity: Hypersensitivity reactions including life-threatening anaphylaxis, can occur during therapy, premedication recommended 30-60 minutes prior to administration.

» Pancreatitis: including haemorrhagic or necrotizing pancreatitis have been reported; Serum amylase and/or lipase levels should be monitored frequently to identify early signs of pancreatic inflammation.

» Haemorrhage: Increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenaemia can occur. Coagulation parameters should be monitored at baseline and periodically during and after treatment. Discontinue treatment for severe life-threatening haemorrhage.

» Thromboembolism: For uncomplicated deep vein thrombosis treat with appropriate antithrombotic therapy. Upon resolution of symptoms consider resuming treatment with continuing antithrombotic therapy. Discontinue treatment permanently for severe life-threatening thrombosis.

» Hyperglycaemia: Continue therapy for uncomplicated hyperglycaemia there is requirement for insulin therapy hold treatment until blood glucose is controlled then resume treatment and do not make up for missed dose.

Hepatic impairment:

» Prior to treatment initiation: Mild to moderate Impairment: No dose adjustment is necessary. Severe impairment: use is contraindicated.

» Hepatotoxicity during treatment:

Total bilirubin > 3 to 10 times ULN withhold treatment until total bilirubin levels decrease to ≤ 1.5 times ULN.

Total bilirubin > 10 times ULN: discontinue and do not make up for missed doses.

Renal impairment: No dose adjustment is necessary.

Pregnancy: Should not be used during pregnancy. Men and women should use effective non oral contraception during treatment and for at least 6 months after discontinuation of treatment.

Breastfeeding: Not recommended for use during breastfeeding and for 1 month after the last dose.

Adverse effects: Infections, Anaemia, coagulopathy, Hypersensitivity, urticaria, hyperglycaemia, hyperlipidaemia, Seizure, peripheral motor neuropathy, Pancreatitis, diarrhoea, abdominal pain, nausea, vomiting, hepatotoxicity and rash.

Interactions with other medicines: Methotrexate, cytarabine, corticosteroids, vincristine

Notes:

» Premedicate patients with paracetamol, an H-1 receptor blocker, and a H-2 receptor blocker 30-60 minutes prior to administration.

Pemetrexed

ATC code: L01BA04

PFI, 500 mg, (vial), LOU5

Indications and dose

Adult

Non-small cell lung cancer (NSCLC), nonsquamous : Intravenous infusion: 500mg/m2 on day 1 of each 21 day cycle in combination with cisplatin for up to 6 cycles. Then maintenance until disease progression or unacceptable toxicity. OR 500mg/m2 in combination with Pembrolizumab and cisplatin or carboplatin for 4 cycles then maintenance in combination with Pembrolizumab or pemetrexed alone until disease progression or unacceptable toxicity.

Malignant pleural mesothelioma: Intravenous infusion: 500 mg/m2 on day 1 of each 21-day cycle in combination with cisplatin for 4 -6 cycles or until disease progression or unacceptable toxicity.

Dosage modifications for toxicity:

» Hematologic toxicity:

Neutrophil count<500/mm3 and platelets≥ 50,000/mm3 hold therapy until neutrophil count≥1500/mm3 and platelets ≥ 100,00/mm3 then resume at 75% of prior dose in subsequent cycles.

Platelets< 50,000/mm3 regardless of neutrophil count hold therapy until platelets ≥ 100,00/mm3 then resume at 75% of prior dose in subsequent cycles.

Platelets< 50,000/mm3 with bleeding regardless of neutrophil count hold therapy until platelets ≥ 100,00/mm3 then resume at 50% of prior dose in subsequent cycles.

» Diarrhoea: Grade 3 or 4 diarrhoea or requiring hospitalisation): Reduce pemetrexed dose to 75% of prior dose.

» Mucositis: Grade 3 or 4 mucositis: Reduce pemetrexed dose to 50% of prior dose.

» Neurotoxicity: For grade 1-2 maintain 100% dose. Grade 3 or 4 permanently discontinue pemetrexed.

» Any Grade 3 or 4 toxicity (excluding mucositis and neurotoxicity): Reduce pemetrexed dose to 75% of prior dose.

Paediatric

Safety and efficacy of pemetrexed in children has not been established.

Contraindications: Hypersensitivity to the active substance or any of the excipients, breastfeeding, concomitant yellow fever vaccine.

Precautions:

» Bone marrow suppression: may cause severe myelosuppression which is often dose limiting. Prophylactic folic acid and vitamin B12 supplements are necessary to reduce haematological toxicity.

» Patients with mild to moderate renal insufficiency (CrCl 45-79mL/min) should avoid taking NSAIDs for 2 days before, on the day of and 2 days following pemetrexed administration.

» Radiation pneumonitis and radiation recall have been reported in patients who have received radiotherapy during or after their pemetrexed therapy and previously received radiotherapy respectively.

Hepatic impairment: No dose adjustments required.

Renal impairment:

» Creatinine clearance ≥45 mL/min: No dosage adjustment necessary.

» Creatinine clearance <45 mL/min: No recommended dose; do not administer.

Pregnancy: Pemetrexed should not be used during pregnancy**.** Women of childbearing age should use effective contraception during treatment and for 6 months following the last dose. Males with female partners should use effective contraception during treatment and for 3 months following the last dose**.**

Breastfeeding: Women should not breastfeed during treatment and for 1 week after the last dose.

Adverse effects: Bone marrow suppression, gastrointestinal toxicities; nausea, vomiting, mucositis, constipation, renal toxicity, fatigue, rash, alopecia.

Interactions with other medicines (*indicates serious):

Concomitant administration of nephrotoxic substances; aminoglycosides, loop diuretics, tubularly secreted drugs; probenecid, penicillin, NSAIDs; ***ibuprofen**, aspirin, oral anticoagulants such as warfarin.

Notes:

» Premedication: oral folic acid 350-1000 micrograms should be taken daily and must be taken one week before the first dose of pemetrexed, during treatment and for 21 days after the last dose of pemetrexed. Intramuscular injection of vitamin B12 1000 micrograms should be given one week before the first dose of pemetrexed then once every three cycles thereafter.

Procarbazine

ATC code: L01XB01

Capsule, 50 mg (as HCl), LOU 5

Indications and dose

Adult and paediatric

Treatment of Hodgkin lymphomas (In combination chemotherapeutic regimens), oral: Procarbazine is usually administered concomitantly with other appropriate cytostatic drugs in repeated four- to six-weekly cycles. In most such combination chemotherapy regimens currently in use, procarbazine is given daily on the first 10–14 days of each cycle in a dosage of 100 mg per square metre of BSA (to nearest 50 mg).

As sole therapeutic agent, oral: Treatment should begin with small doses that are increased gradually up to a maximum daily dose of 250 or 300 mg divided as evenly as possible throughout the day.

Initial dosage scheme:

1st day: 50 mg

2nd day: 100 mg

3rd day: 150 mg

4th day: 200 mg

5th day: 250 mg

6th day and thereafter: 250–300 mg

Treatment should be continued with 250 or 300 mg daily until the greatest possible remission has been obtained, after which a maintenance dose is given.

Maintenance dose: 50–150 mg daily. Treatment should be continued until a total dose of at least 6 g has been given. Otherwise, a negative result is not significant.

Elderly: Procarbazine should be used with caution in the elderly. Patients in this group should be observed very closely for signs of early failure or intolerance of treatment. The dose should be adjusted according to:

- The chemotherapy protocol used
- The functional state of the bone marrow
- Previous chemo- and radiotherapy cycles
- The myelosuppressive effect of other cytostatics used

Contraindications: Pre-existing severe leucopenia or thrombocytopenia from any cause, severe hepatic or renal damage. Procarbazine should not be used in the management of non-malignant disease. Procarbazine is contraindicated during the first trimester of pregnancy and during breastfeeding. Hypersensitivity to the active substance (Procarbazine) or to any of the excipients.

Precautions: Procarbazine should be avoided in patients with severe hepatic or renal disease. Its use should be avoided if CrCl is less than 10 mL/min. Caution is also advised in cardiovascular or cerebrovascular disease, phaeochromocytoma, or epilepsy.

Regular blood counts are of great importance due to the possibility of bone-marrow suppression. If during the initial treatment the total white cell count falls to 3,000 per mm3 or the platelet count to 80,000 per mm3, treatment should be suspended temporarily until the leucocyte and/or platelet levels recover, when therapy with the maintenance dose may be resumed.

Treatment should be interrupted on the appearance of allergic skin reactions.

Live vaccines should not be given during or within at least 6 months of treatment with immunosuppressive chemotherapy or radiotherapy for malignant disease.

Adverse effects: Loss of appetite, nausea and vomiting, leucopenia, thrombocytopenia

Interactions with other medicines:

- Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, carboplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.
- Antiepileptics: Increased risk of hypersensitivity reactions when given with procarbazine
- Increased risk of serotonin syndrome on concurrent use with agents having similar effects including: Fentanyl, fluoxetine, granisetron, imipramine, linezolid, lithium, methadone, ondansetron, pethidine, tramadol

Temozolomide

ATC code: L01AX03

Capsule,20mg, 100mg, LOU 5

Indications and dose

Adult

Treatment of newly diagnosed glioblastoma multiforme

Concomitant phase, oral: 75mg/m2 once daily for 42 days in combination with radiotherapy.

Maintenance phase four weeks after concomitant phase, oral: 150 mg/m2 daily day 1 to 5, then 200 mg/m2 day 1 to 5 of a 28-day treatment cycle for cycle 2 to cycle 6.

Treatment of refractory anaplastic astrocytoma, oral: 150mg/m2 once daily on days 1 to 5, then 200 mg/m2 on day 1 to 5 of a 28 day treatment cycle.

Paediatric

Treatment of recurrent or progressive malignant glioma in patients 3 years or older: Oral, 150mg/m2 once daily on days 1 to 5, then 200 mg/m2 on day 1 to 5 of a 28-day treatment cycle.

Dosage modifications for toxicity in concomitant phase:

- Haematological toxicity (weekly monitoring): If neutrophil count ≥ 500/mm3 and< 1500/mm3 or platelet count ≥ 10,000/mm3 and <100,000/mm3 interrupt treatment. When Neutrophil count >1500/mm3 and platelet count >100,000/mm3 resume temozolomide.
- If neutrophil count <500/mm3 or platelet count < 10,000/mm3 discontinue temozolomide.
- Non haematological (except for alopecia, nausea, vomiting): Grade 2 toxicity interrupt treatment and resume if toxicity resolved to ≤ grade 1. Permanently discontinue for grade 3 or 4 toxicity.

Dosage modifications for toxicity in maintenance phase:

- Haematological toxicity: Neutrophil count <1000/mm3 or platelet count <50,000/mm3 interrupt treatment when Neutrophil count >1500/mm3 and platelet count >100,000/mm3 resume temozolomide with a decrease in dose by 50 mg/m2/day. Permanently discontinue if unable to tolerate a dose of 100mg/m2/day.
- Non haematological (except for alopecia, nausea, vomiting): Grade 3 toxicity interrupt treatment and resume if toxicity resolved to ≤ grade 1. Resume temozolomide with a decrease in dose by 50 mg/m2/day. Permanently discontinue if unable to tolerate a dose of 100mg/m2/day.

Contraindications: Hypersensitivity to the active substance or any of the excipients, hypersensitivity to dacarbazine, severe myelosuppression.

Precautions:

- *Pneumocystis jirovecii* pneumonia (PCP) risk increased in patients receiving corticosteroids, those receiving concomitant radiotherapy or with longer temozolomide treatment. Provide PCP prophylaxis for those on concomitant radiotherapy.
- Bone marrow suppression: Myelosuppression with fatal outcomes have been reported.
- Hepatotoxicity: Reports of liver function abnormalities, hepatitis and hepatic failure have been reported.
- Secondary malignancies: Cases of myelodysplastic syndromes and secondary malignancies and myeloid leukaemia have been reported.

Hepatic impairment: No dose adjustments required, use in caution with severe hepatic impairment.

Renal impairment: No dose adjustments required, use in caution with severe renal impairment.

Pregnancy: Should not be administered to pregnant women. Women of childbearing age should use effective contraception during treatment and for 6 months following the last dose males with female partners should use effective contraception during treatment and for 3 months following the last dose.

Breastfeeding: Women should not breastfeed during treatment and for at least one week after the final dose.

Adverse effects: lymphopenia, neutropenia, hyperglycaemia, nausea, vomiting, constipation, anorexia, headache, fatigue, convulsions, hemiparesis and rash,

Interactions with other medicines (*indicates serious): Valproic acid, palifermin tofacitinib, deferiprone and denosumab*.

Notes:

- Administration: Administer consistently either with or without food.

Tioguanine

ATC code: L01BB03

Solid oral dose form, 40 mg [c], LOU 5

Indications and dose

Adult

Acute myeloid leukaemia, acute lymphocytic leukaemia, and metronomic chemotherapy, oral: Usual dosage is between 100 and 200 mg/m2 BSA per day, but the exact dose and duration of administration will depend on the nature and dosage of other cytotoxic drugs given in conjunction with tioguanine.

Paediatric

Acute myeloid leukaemia, acute lymphocytic leukaemia, and metronomic chemotherapy, oral

Child all ages: Usual dosage is between 100 and 200 mg/m2 BSA per day, but the exact dose and duration of administration will depend on the nature and dosage of other cytotoxic drugs given in conjunction with tioguanine.

Contraindications: In view of the seriousness of the indications there are no absolute contraindications.

Precautions: In all cases, patients in remission should not receive live organism vaccines until at least 3 months after their chemotherapy treatment has been completed.

Tioguanine is not recommended for maintenance therapy or similar long-term continuous treatments due to the high risk of liver toxicity associated with vascular endothelial damage.

Tioguanine therapy should be discontinued in patients with evidence of liver toxicity as reversal of signs and symptoms of liver toxicity have been reported upon withdrawal.

Pregnancy: The use of tioguanine should be avoided whenever possible during pregnancy, particularly during the first trimester

Breastfeeding: It is suggested that mothers receiving tioguanine should not breastfeed.

Adverse effects: bone marrow suppression, liver problems, inflammation of the mouth

Interaction with other medicinal products and other forms of interaction

- Vaccines: Vaccination with live organism vaccines are not recommended in immunocompromised individuals
- Other myelotoxic substances or radiation therapy: During concomitant administration of other myelotoxic substances or radiation therapy, the risk of myelosuppression is increased.
- Aminosalicylate derivatives: As there is *in vitro* evidence that aminosalicylate derivatives (e.g., olsalazine, mesalazine or sulfasalazine) inhibit the thiopurine methyltransferase enzyme, they should be administered with caution to patients receiving concurrent tioguanine therapy

Topotecan

ATC code: L01CE01

Injection, 2.5 mg, LOU 5

Indications and dose

Adult

Treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy, combination therapy with Cisplatin for stage IV-B, recurrent or persistent cervical cancer which cannot be treated with surgery and/or radiation therapy, and metastatic ovarian cancer after failure of initial or subsequent chemotherapy

Prior to administration of the first course of topotecan, patients must have a baseline neutrophil count of ≥1.5 × 10^9/L, a platelet count of ≥100 × 10^9/L, and a haemoglobin level of ≥9 g/dL (after transfusion, if necessary).

Ovarian and small cell lung carcinoma, by IV infusion

- *Initial dose:* Recommended dose of topotecan is 1.5 mg/m2 BSA per day administered by IV infusion over 30 minutes daily for five consecutive days with a three-week interval between the start of each course. If well tolerated, treatment may continue until disease progression
- *Subsequent doses:* Topotecan should not be readministered unless the neutrophil count is ≥1 × 109/L, the platelet count is ≥100 × 109/L, and the haemoglobin level is ≥9 g/dL (after transfusion, if necessary).

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count <0.5 × 109/L) for seven days or more or severe neutropenia associated with fever or infection or who have had treatment delayed due to neutropenia, the dose should be reduced by 0.25 mg/m2/day to 1.25 mg/m2/day (or subsequently down to 1.0 mg/m2/day if necessary). Doses should be similarly reduced if the platelet count falls below 25 × 109/L.

Cervical carcinoma, by IV infusion

- *Initial dose:* Recommended dose of topotecan is 0.75 mg/m2/day administered as a 30-minute IV infusion on days 1, 2, and 3. Cisplatin is administered as an IV infusion on day 1 at a dose of 50 mg/m2/day and following the topotecan dose. This treatment schedule is repeated every 21 days for six courses or until progressive disease.
- *Subsequent doses:* Topotecan should not be readministered unless the neutrophil count is ≥1.5 × 109/L, the platelet count is ≥100 × 109/L, and the haemoglobin level is ≥9 g/dL (after transfusion, if necessary).

Standard oncology practice for managing neutropenia is either to administer topotecan with other medicinal products (e.g., G-CSF) or to reduce the dose to maintain neutrophil counts.

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count <0.5 × 109/L) for seven days or more or severe neutropenia associated with fever or infection or who have had treatment delayed due to neutropenia, the dose should be reduced by 20% to 0.60 mg/m2/day for subsequent courses (or subsequently down to 0.45 mg/m2/day if necessary). Doses should be similarly reduced if the platelet count falls below 25 x 109/L.

Contraindications: Severe hypersensitivity to the active substance or to any of the excipients. Breastfeeding. Severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils < 1.5 × 109/L and/or a platelet count of <100 × 109/L.

Precautions: In patients presenting with fever, neutropenia and a compatible pattern of abdominal pain, the possibility of neutropenic colitis should be considered. Patients should be monitored for pulmonary symptoms indicative of Interstitial Lung Disease (ILD) (e.g., cough, fever, dyspnoea and/or hypoxia), and topotecan should be discontinued if a new diagnosis of ILD is confirmed. Topotecan monotherapy and topotecan in combination with cisplatin are commonly associated with clinically relevant thrombocytopenia. This should be taken into account when prescribing topotecan, e.g., if patients at increased risk of tumour bleeds are considered for therapy.

Pregnancy: If topotecan is used during pregnancy, or if the patient becomes pregnant during therapy with topotecan, the patient must be informed of the potential hazards to the foetus.

Breastfeeding: Topotecan is contraindicated during breastfeeding

Adverse effects: Myelosuppression, specifically neutropenia, leukopenia, anemia, and thrombocytopenia. Diarrhea, nausea, vomiting, stomatitis, and constipation. Increased susceptibility to infections, Asthenia.

Interactions with other medicines:

- Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, carboplatin, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine,

trimethoprim, vincristine, vinblastine, zidovudine.

- Increased concentration of topotecan:
  - Antifungals: ketoconazole, fluconazole
  - Antiarrythmics: Amiodarone
  - CCBs: diltiazem, verapamil
  - Ciclosporin
  - Grapefruit
  - Protease Inhibitors: ritonavir, lopinavir
  - Macrolides: clarithromycin, erythromycin
- Decreased concentration of topotecan:
  - Antiepileptics: carbamazepine, phenytoin, phenobarbitone
  - Efavirenz, Nevirapine
  - Rifampicin
  - St Johns wort (*Hypericum perforatum*)

Vinblastine

ATC code: L01CA01

Injection, 1 mg/mL (10-mL vial), LOU 5

Indications and dose

Adult

Disseminated Hodgkin and non-Hodgkin lymphomas, advanced testicular carcinoma, breast carcinoma, palliative treatment of Kaposi sarcoma, trophoblastic tumours, Letterer-Siwe disease, IV: 6 mg/m2, usually administered no more frequently than once every seven days. For testicular tumours, the dosage may be increased to 0.2 mg/kg administered on each of two consecutive days every three weeks.

Contraindications: Hypersensitivity to the active substance or to any of the excipients

For IV use only. Fatal if given by other routes. Vinblastine sulphate is contraindicated in patients who are leucopenic. It should not be used in the presence of bacterial infection. Such infections should be brought under control with antiseptics or antibiotics before the initiation of therapy with vinblastine sulphate.

Precautions: Vinblastine SHOULD NOT BE GIVEN intramuscularly, subcutaneously or intrathecally. Syringes containing this product should be overlabelled with the intrathecal warning label provided – **'FOR IV USE ONLY. FATAL IF GIVEN BY OTHER ROUTES'.**

Patients should be carefully monitored for infection until the white cell count has returned to normal levels, if leucopoenia with less than 2000 WBCs per mm3 occurs following a dose of vinblastine sulphate.

Pregnancy: Vinblastine may cause foetal toxicity when administered to pregnant women

Breastfeeding: A decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Adverse effects: Leucopenia, thrombocytopaenia, anaemia, numbness, paraesthesias, peripheral neuritis, mental depression, loss of deep tendon reflexes, headache, convulsions, MI, cerebrovascular accident.

Interaction with other medicinal products and other forms of interaction

- When chemotherapy is being given in conjunction with radiation therapy through portals which include the liver, the use of vinblastine should be delayed until radiation therapy has been completed.
- Vinblastine used as part of a combination regimen with mitomycin may result in acute respiratory distress and pulmonary infiltration. Vinblastine should not be re-administered.
- Co-administration of cisplatin has been reported to cause higher plasma concentrations of vinblastine.
- There have been reports of Raynaud's phenomenon and gangrene following co-administration of vinblastine and bleomycin, and of other vascular events (such as MI and cerebrovascular accident) following combined treatment with vinblastine, bleomycin and cisplatin.
- Erythromycin may increase the toxicity of vinblastine.
- Serum levels of anticonvulsants may be reduced by cytotoxic drug regimes, which include vinblastine.
- Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic CYP450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vinblastine sulphate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of adverse effects.

Vincristine

ATC code: L01CA02

Injection (PFI or solution for injection), 1 mg (as sulphate) vial, LOU 5

Indications and dose

Adult

Use in treatment of diffuse large B-cell lymphoma, gestational trophoblastic neoplasia, Hodgkin lymphoma, Kaposi sarcoma, follicular lymphoma, retinoblastoma, rhabdomyosarcoma, Ewing sarcoma, acute lymphoblastic leukaemia, nephroblastoma (Wilms tumour), Burkitt lymphoma, IV: 1.4 to 1.5 mg/m2 up to a maximum weekly dose of 2 mg, administered intravenously at weekly intervals

Elderly: The normal adult dose is still appropriate in the elderly.

Paediatric

Child weighing 10 kg or less: Starting dose 0.05 mg/kg administered as a weekly IV injection

Child: 1.4 to 2 mg/m2 given on a weekly basis with a maximum weekly dose of 2 mg.

Contraindications: Hypersensitivity to vincristine sulphate or to any of the excipients, patients with the demyelinating form of Charcot-Marie-Tooth syndrome. As Vincristine Sulphate solution for injection contains benzyl alcohol it must not be given to premature babies or neonates.

Precautions: Vincristine sulphate **SHOULD NOT be given by intrathecal, IM or SC injection**.

Syringes containing this product should be labelled **'VINCRISTINE FOR IV USE ONLY. FATAL IF GIVEN BY OTHER ROUTES'**.

Pregnancy: Vincristine can cause foetal harm following maternal or paternal exposure.

Breastfeeding: A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from vincristine sulphate therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Adverse effects: change in sensation, hair loss, constipation, difficulty walking, and headaches, neuropathic pain, lung damage, low WBCs

Interaction with other medicinal products and other forms of interaction

- The neurotoxicity of vincristine sulphate may be additive with that of isoniazid and other drugs acting on the nervous system.
- Acute shortness of breath and severe bronchospasm when used in combination with mitomycin-C and may be serious when there is pre-existing pulmonary dysfunction. The onset may be within minutes or several hours after the vinca is injected and may occur up to 2 weeks following the dose of mitomycin. Progressive dyspnoea, requiring chronic therapy, may occur. Vincristine should not be re-administered.
- Phenytoin: vincristine reduces blood levels of phenytoin to increase seizure activity. Dosage adjustment of phenytoin, based on serial blood level monitoring, may need to be made when it is used in combination with vincristine.
- Concurrent administration of vincristine sulphate with itraconazole or fluconazole (known inhibitor of the metabolic pathway) have been reported to cause an earlier onset and/or an increased severity of neuromuscular adverse effects, inducers like St. John's wort should be given cautiously. This interaction is presumed to be related to inhibition of the metabolism of vincristine.
- When vincristine sulphate is used in combination with L-asparaginase, it should be given 12 to 24 hours before administration of the enzyme in order to minimize toxicity, since administering L-asparaginase first may reduce hepatic clearance of vincristine.
- When chemotherapy is being given in conjunction with radiation therapy through portals which include the liver, the use of vincristine should be delayed until radiation therapy has been completed.
- Vincristine sulphate appears to increase the cellular uptake of methotrexate by malignant cells and this principle has been applied in high-dose methotrexate therapy.
- Severe hepatotoxicity, including veno-occlusive disease has been reported in patients treated with a combination of vincristine and dactinomycin for renal carcinoma.

Vinorelbine

ATC code: L01CA04

Injection, 10 mg/mL (1-mL vial, 5-mL vial), LOU 5

Indications and dose

Adult

Stage 3 or 4 non-small cell lung cancer, advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen, IV: 25–30 mg/m² once weekly. It may be administered by a:

- Slow bolus (6–10 minutes) after dilution: In 20–50 mL of sodium chloride 9 mg/mL (0.9%) solution for injection **OR** in 5% (w/v) glucose solution for injection **OR**
- Short infusion (20–30 minutes) after dilution: in 125 mL of sodium chloride 9 mg/mL (0.9%) solution for injection **OR** in 5% (w/v) glucose solution for injection

Administration should always be followed by a sodium chloride 9 mg/mL (0.9%) infusion with at least 250 mL to flush the vein.

In combination with other cytostatic agents the exact dose should be taken from the treatment protocol.

Contraindications: Known hypersensitivity to vinorelbine or other vinca alkaloids, or to any of the excipients. Neutrophil count < 1500/mm3 or severe infection current or recent (within 2 weeks). Platelet count < 100000/mm3. In combination with yellow fever vaccine

Precautions: Close haematological monitoring should be undertaken during treatment (determination of haemoglobin level and the leukocyte, neutrophil and platelet counts on the day of each new administration). If the neutrophil count is below 1500/mm3and/or the platelet count is below 100000/mm3, then the treatment should be delayed until recovery. Should not be given concomitantly with radiotherapy if the treatment field includes the liver. Combination of vinorelbine with phenytoin (like all cytotoxics) and with itraconazole (like all vinca alkaloids) is not recommended.

Pregnancy: Vinorelbine is contraindicated in pregnancy.

Breastfeeding: Breastfeeding must be discontinued before starting treatment with vinorelbine

Adverse effects: stomatitis, nausea and vomiting, bacterial infections, viral infections, neutropenia, leucopenia, alopecia, diarrhea.

Interaction with other medicinal products and other forms of interaction

- Concomitant use contraindicated
- Yellow fever vaccine: as with all cytotoxics, risk of fatal generalized vaccine disease
- Concomitant use not recommended
- Live attenuated vaccines: (for yellow fever vaccine, see concomitant use contraindicated) as with all cytotoxics, risk of generalized vaccine disease, possibly fatal. This risk is increased in patients already immunodepressed by their underlying disease. It is recommended to use an inactivated vaccine when one exists

(e.g., poliomyelitis)

- Phenytoin: as with all cytotoxics, risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.
- Itraconazole: as with all vinca-alkaloids, increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.
- Concomitant use to take into consideration
- Cisplatin: There is no mutual pharmacokinetic interaction when combining vinorelbine with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with vinorelbine use in combination with cisplatin is higher than associated with vinorelbine single agent.
- Mitomycin C: risk of bronchospasm and dyspnoea are increased, in rare case an interstitial pneumonitis was observed.
- Ciclosporin, tacrolimus: excessive immunodepression with risk of lymphoproliferation.
- As vinca alkaloids are known substrates for P_glycoprotein, and in the absence of specific study, caution should be exercised when combining vinorelbine with strong modulators of this membrane transporter.
- The combination of vinorelbine with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.
- As CYP3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g., azole antifungals such as ketoconazole and itraconazole) could increase blood concentrations of vinorelbine and combination with strong inducers of this isoenzyme (e.g., rifampicin, phenytoin) could decrease blood concentrations of vinorelbine.
- Anticoagulant treatment: as with all cytotoxics, the frequency of INR (International Normalised Ratio) monitoring should be increased due to the potential interaction with oral anticoagulants and increased variability of coagulation in patients with cancer.

9.2.2. Targeted Therapies

All-Trans Retinoid Acid (ATRA)

ATC code: Not assigned

Capsule, size/strength: 10 mg, LOU 5

Indications and dose

Adult

Acute promyelocytic leukemia, oral: For all therapy phases a total daily dose of 45 mg/m² BSA divided in two equal doses is recommended for adults and elderly APL patients. This is approximately 8 capsules per adult dose (one capsule contains 10 mg tretinoin).

Paediatric

The optimal dose of tretinoin has not yet been established. In an attempt to reduce tretinoin-related toxicity, the daily dose administered to children can be reduced to 25 mg/m2. Dose reduction should be particularly considered for children with toxicity symptoms, such as intractable headache.

Contraindications: Hypersensitivity to tretinoin, retinoids, soya, peanut or to any of the excipients. Tretinoin is teratogenic. It is contraindicated during breastfeeding.

Combination with vitamin A, tetracyclines, retinoids.

Adverse effects: shortness of breath, headache, numbness, depression, skin dryness, itchiness, hair loss, vomiting, muscle pains, and vision changes, high WBC counts, blood clots

Bevacizumab

ATC code: L01XC07

Injection, 25 mg/mL (4-mL,16-ml,vial), LOU 5

Indications and dose

Adult

- *Metastatic colorectal cancer: Intravenous infusion,*5 mg/kg every 2 weeks or 7.5mg/kg every 3 weeks in combination with a fluoropyrimidine plus irinotecan or oxaliplatin-based chemotherapy
- *Cervical cancer: intravenous infusion,* 15 mg/kg once every 3 weeks in combination with chemotherapy or monotherapy until disease progression or unacceptable toxicity.
- *Advanced or metastatic renal cell carcinoma: Intravenous infusion,* 10 mg/kg every 2 weeks as monotherapy or in combination with interferon until disease progression or unacceptable toxicity.
- *Recurrent glioblastoma: Intravenous infusion,* 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity.
- *Unresectable or metastatic hepatocellular carcinoma: Intravenous infusion,* 15 mg/kg every 3 weeks in combination with atezolizumab until disease progression or unacceptable toxicity.

Paediatric

No evidence for use in Malignancy.

For use in *Retinopathy of prematurity, intravitreal, See Section 22.6*

Contraindications: hypersensitivity to Bevacizumab, murine products, or any component of the formulation, pregnancy, and breastfeeding.

Precautions: Heart disease, stroke, or bleeding disorder

- Gastrointestinal perforations and fistulae: Therapy should be permanently discontinued.
- Wound healing complications: Therapy should

not be initiated at least 28 days following major surgery or until the wound is fully healed.

» Hypertension: Therapy should be permanently discontinued in case of uncontrolled hypertension, hypertensive crisis or hypertensive encephalopathy.

» Proteinuria: Therapy should be permanently discontinued in patients who develop nephrotic syndrome and withheld in proteinuria ≥2g per 24 hours until recovery.

» Thromboembolism: Therapy should be permanently discontinued in patients who develop pulmonary embolism and life-threatening thromboembolic reactions.

Hepatic impairment: There are no dose adjustments provided in the manufacturer's labelling.

Renal impairment: There are no dose adjustments provided in the manufacturer's labelling.

Pregnancy: Should not be used during pregnancy. Women of childbearing age should use effective contraception during treatment and for 6 months following the last dose.

Breastfeeding: Breast-feeding should be discontinued during treatment and for at least 6 months after the final dose.

Adverse effects: cataract formation, glaucoma, bleeding, hypotony, damage to the retina or cornea, endophthalmitis Hypertension, venous thromboembolism, hyperglycaemia, hypoalbuminemia, abdominal pain, dysgeusia, proteinuria, neutropenia, thrombocytopenia, dysarthria, pulmonary haemorrhage, arthralgia, back pain, and postoperative wound complication.

Interactions with other medicines: palifermin, ropeginterferon alfa 2b, sunitinib

Notes:

» Not to be mixed with dextrose-containing solutions.

» Bevacizumab can be used for other indications as guided by a specialist.

Bortezomib

ATC code: L01XG01

Powder for injection, 3.5-mg vial, LOU 5

Indications and dose

Adult

Previously untreated multiple myeloma, by IV: Administer in combination with prednisone and melphalan as part of 6-wk treatment cycles for 9 cycles

Cycles 1–4 (twice weekly): 1.3 mg/m² IV/SC on days 1, 4, 8, 11, 22, 25, 29, and 32

Cycles 5–9 (once weekly): 1.3 mg/m² IV/SC on days 1, 8, 22, and 29

Relapsed multiple myeloma, IV: 1.3 mg/m²/dose IV/SC twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12–21)

» Therapy extending beyond 8 cycles: Standard or maintenance schedule of once weekly for 4 weeks (days 1, 8, 15, and 22) followed by a 13-day rest period (days 23 to 35)

Retreatment: Indicated for retreatment of adults with multiple myeloma who had previously responded to bortezomib and relapsed at least 6 months following completion of prior bortezomib treatment

» Treatment may be started at the last tolerated dose

» Administer twice weekly for 2 weeks (days 1, 4, 8, 11) followed by a 10-day rest period (days 12 to 21)

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Hypersensitivity to the active substance, to boron, or to any of the excipients. Acute diffuse infiltrative pulmonary and pericardial disease.

Precautions: Bortezomib **SHOULD NOT be administered intrathecally**. Patients who experience constipation should be closely monitored. CBCs with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate

Herpes zoster virus reactivation: Antiviral prophylaxis is recommended in patients being treated with bortezomib.

HBV reactivation and infection: When rituximab is used in combination with bortezomib, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Antiviral prophylaxis should be considered.

Adverse effects: nausea, diarrhea, tiredness, low platelets, fever, numbness, low WBCs, shortness of breath, rash, abdominal pain, low blood pressure, tumour lysis syndrome, heart failure, and reversible posterior leukoencephalopathy syndrome

Interactions with other medicines:

» Increased risk of myelosuppression on concurrent use with other myelosuppressive agents including: Azathioprine, bleomycin, carbimazole, capecitabine, carboplatin, cisplatin, chlorambucil, cyclophosphamide, docetaxel, doxorubicin, epirubicin, ethosuccimide, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, linezolid, methotrexate, mercaptopurine, mycophenolate, olanzapine, oxaliplatin, paclitaxel, rituximab, propylthiouracil, sulphamethoxazole, sulfadiazine, trimethoprim, vincristine, vinblastine, zidovudine.

» Increased risk of peripheral neuropathy on concurrent use with other agents causing it, including: Cisplatin, isoniazid, lamivudine, metronidazole, nitrofurantoin, carboplatin, paclitaxel, phenytoin, stavudine, vincristine, vinblastine, thalidomide.

» Drugs that increase concentration of bortezomib:

- Antifungals: ketoconazole, fluconazole
- Macrolides. Avoid or adjust dose

» Drugs that decrease concentration of bortezomib:

- Antiepileptics (phenobarbitone, carbamazepine, phenytoin)
- Rifampicin

Gefitinib

ATC code: L01EB01

Tablet, 250 mg, LOU 5

Indications and dose

Adult

EGFR mutation-positive advanced non-small cell lung cancer: Use as alternative to erlotinib; one 250 mg tablet once a day

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Hypersensitivity to the active substance or to any of the excipients

Adverse effects: acne-like rash, diarrhoea, nausea, vomiting, anorexia, stomatitis, dehydration, skin reactions, paronychia, asymptomatic elevations of liver enzymes, asthenia, conjunctivitis, blepharitis.

Interactions with other medicinal products

» CYP3A4 inducers may increase metabolism of gefitinib and decrease gefitinib plasma concentrations. Therefore, concomitant administration of CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampicin, barbiturates or herbal preparations containing St John's wort/*Hypericum perforatum*) may reduce efficacy of the treatment and should be avoided

» Patients taking warfarin and gefitinib concomitantly should be monitored regularly for changes in PT or INR.

» Medicinal products that cause significant sustained elevation in gastric pH, such as proton-pump inhibitors and h2-antagonists may reduce bioavailability and plasma

» concentrations of gefitinib and, therefore, may reduce efficacy. Antacids if taken regularly close in time to administration of gefitinib may have a similar effect.

Ibrutinib

ATC code: L01EL01

Capsule, 140mg, LOU 5

Indications and dose

Adult

Treatment of Chronic lymphocytic leukaemia (CLL): Oral, 420 mg once daily.(As monotherapy or in combination with rituximab, or bendamustine and rituximab)

Dosage modifications for toxicity:

» Cardiac arrhythmias: Grade 3 toxicity first occurrence; restart at 280mg for second occurrence and grade 4 toxicity regardless of occurrence discontinue treatment.

» Heart failure: Grade 2 toxicity first occurrence; restart at 280 mg for second occurrence and grade 3 and 4 toxicity regardless of occurrence discontinue treatment.

» Haematological toxicity: Grade 3 neutropenia or febrile neutropenia or any grade 4 haematological toxicity; withhold until toxicity resolves to grade 1 then reinitiate as shown in the table below.

» Non-haematological toxicities except cardiac failure and heart failure: Grade 3 and 4 toxicities; withhold until toxicity resolves to grade 1 then reinitiate as shown in the table below:

Toxicity occurrence	CLL dose modification after recovery
First	Restart at 420 mg
Second	Restart at 280 mg
Third	Restart at 140 mg
Fourth	Discontinue treatment

Paediatric: There is no indication for use in chronic lymphocytic leukaemia in paediatrics.

Contraindications: Hypersensitivity to the active substance or any of the excipients.

Precautions:

» Hypertension: Has been reported with a median time to onset of 5.9 months that required initiation of antihypertensive therapy. Monitor for the same.

» Second primary malignancies: Patients have developed non melanoma skin carcinoma.

» Haemorrhage: fatal major haemorrhage has occurred including intracranial haemorrhage and gastrointestinal haemorrhage.

» Cardiac arrhythmias and cardiac failure: Serious and fatal cardiac arrhythmias and cardiac failure have been reported.

» Cytopenia and infections: Grade 3 or 4 cytopenia (neutropenia, thrombocytopenia, and anaemia) were reported including opportunistic infections such as *Pneumocystis jirovecii* pneumonia.

» Splenic rupture: Cases of splenic rupture have been reported following discontinuation of treatment.

Hepatic impairment:

Mild liver impairment (Child-Pugh class A): Reduce dose to 280 mg daily and monitor for toxicities.

Moderate liver impairment (Child-Pugh class B): Reduce dose to 140 mg daily and monitor for toxicities.

Severe hepatic impairment (Child-Pugh class C): Use not recommended.

Renal impairment:

» Creatinine clearance ≥30 mL/min: No dosage

adjustment is necessary.

» Creatinine clearance <30 mL/min: No recommended dose; use with caution.

» End-stage renal disease requiring dialysis: No data available.

Pregnancy: Should not be used during pregnancy. Women of childbearing age should use effective contraception during treatment and for 1 month following the last dose males with female partners should use effective contraception during treatment and for 1 month following the last dose.

Breastfeeding: Breast-feeding should be discontinued during treatment and for at least one week after the final dose.

Adverse effects: Diarrhoea, neutropenia, lymphocytosis, thrombocytopenia, rash, nausea, arthralgia, and upper respiratory tract infection, pneumonia, rash, nausea, musculoskeletal pain, haemorrhage, hypertension, cardiac failure, atrial fibrillation, dizziness, headache, blurred vision, hepatic failure, diarrhoea, dyspepsia, stomatitis, constipation, and increased serum creatinine.

Interactions with other medicines (*indicates serious):

» Strong CYP3A4 inhibitors* (examples: ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, cobicistat, voriconazole and posaconazole) concurrent use should be avoided. If strong CYP3A4 inhibitor must be used, reduce the ibrutinib dose to 140 mg for the duration of the inhibitor use or withhold ibrutinib temporarily (for 7 days or less).

» Moderate CYP3A4 inhibitors* (examples: fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone and dronedarone). Reduce ibrutinib dose to 280 mg for the duration of the inhibitor use.

» Strong and moderate CYP3A4 inducers*(examples: rifampicin, carbamazepine, phenytoin, St John's Wort) Avoid concurrent use.

» P-glycoprotein or BCRP substrates such as digoxin or methotrexate and should be taken at least 6 hours before or after ibrutinib to minimise the potential for an interaction in the gastrointestinal tract.

Notes:

» Ibrutinib can be used for other indications as guided by a specialist.

» Co-administration of grapefruit and Seville oranges should be avoided as they contain ingredients with CYP3A4 inhibition.

» When administering ibrutinib in combination with anti-CD20 therapy, it is recommended to administer ibrutinib prior to anti-CD20 therapy when given on the same day.

» If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra tablets to make up the missed dose.

Imatinib

ATC code: L01EA01

Tablet, 400 mg (as mesylate), LOU 5

Indications and dose

Adult

Chronic myeloid leukaemia (CML) in chronic phase after failure with interferon alfa, oral: 400 mg once daily, increased if necessary up to 800 mg daily in 2 divided doses.

CML is considered in the chronic phase when all of the following criteria are met:

» Blasts <15% in blood and bone marrow

» Peripheral blood basophils <20%

» Platelets >100 × 109/L

CML in accelerated phase or in blast crisis, oral: 600 mg once daily, then increased if necessary up to 800 mg daily in 2 divided doses

CML is considered in the accelerated phase by the presence of any of the following:

» Blasts ≥15% but <30% in blood or bone marrow

» Blasts plus promyelocytes ≥30% in blood or bone marrow (providing <30% blasts)

» Peripheral blood basophils ≥20%

» Platelets <100 × 109/L unrelated to therapy

Blast crisis is defined as blasts ≥30% in blood or bone marrow or extramedullary disease other than hepatosplenomegaly.

Newly diagnosed acute lymphoblastic leukaemia (in combination with other chemotherapy), Monotherapy for relapsed or refractory acute lymphoblastic leukaemia, oral: 600 mg once daily

Treatment of c-kit (CD117)-positive unresectable or metastatic malignant GI stromal tumours (GIST), adjuvant treatment following resection of c-kit (CD117)-positive GIST, in patients at significant risk of relapse, treatment of myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene rearrangement, oral: 400 mg once daily

Treatment of unresectable dermatofibrosarcoma protuberans, recurrent or metastatic dermatofibrosarcoma protuberans in patients who cannot have surgery, oral: 800 mg daily in 2 divided doses

Advanced hypereosinophilic syndrome and chronic eosinophilic leukaemia, oral: 100–400 mg once daily

Paediatric

» *Newly diagnosed Philadelphia-chromosome positive CML when bone marrow transplantation is not considered first-line treatment*

» *Philadelphia-chromosome-positive CML in chronic phase after failure of interferon alfa, or in accelerated phase, or in blast crisis*

» *Newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukaemia in combination with chemotherapy, oral, (consult local protocol)*

Child <2 years of age: There is no experience with children of this age.

Dosing guidance

A dose of 340 mg/m2 daily is recommended for children with chronic phase CML and advanced phase CML (not to exceed the total dose of 800 mg). Treatment can be given as a once daily dose or alternatively the daily dose may be split into two administrations, one in the morning and one in the evening.

Dose increases from 340 mg/m2 daily to 570 mg/m2 daily (not to exceed the total dose of 800 mg) may be considered in children in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances:

- Disease progression (at any time)
- Failure to achieve a satisfactory haematological response after at least 3 months of treatment
- Failure to achieve a cytogenetic response after 12 months of treatment
- Loss of a previously achieved haematological and/or cytogenetic response.

Contraindications: Hypersensitivity to the active substance or to any of the excipients

Precautions: Cardiac disease, hepatitis B infection. History of renal failure, risk factors for heart failure, carriers of HBV should be closely monitored for signs and symptoms of active infection throughout treatment and for several months after stopping treatment, expert advice should be sought for patients who test positive for HBV and in those with active infection.

Hepatic impairment: max. 400 mg once daily, consider further dose reduction if not tolerated

Renal impairment: dose adjustments maximum starting dose 400 mg daily if CrCl less than 60 mL/min, reduce dose further if not tolerated.

Pregnancy: Imatinib should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breastfeeding: Women should not breastfeed during treatment and for at least 15 days after stopping treatment with imatinib.

Conception and contraception: effective contraception required during treatment.

Adverse effects: vomiting, diarrhea, muscle pain, headache, and rash, fluid retention, GI bleeding, bone marrow suppression, liver problems, and heart failure. Common or very common: Alopecia, anaemia, appetite abnormal, asthenia, bone marrow disorders, chills, constipation, cough, diarrhoea, dizziness, dry eye, dry mouth, dyspnoea, excessive tearing, eye inflammation, fever, fluid imbalance, flushing, GI discomfort, GI disorders, haemorrhage, headaches, insomnia, joint disorders, muscle complaints, nausea, neutropenia, oedema, pain, photosensitivity reaction, sensation abnormal, skin reactions, sweat changes, taste altered, thrombocytopenia, vision blurred, vomiting, weight changes. Uncommon: Anxiety, arrhythmias, ascites, breast abnormalities, broken nails, burping, chest pain, CNS haemorrhage, congestive heart failure, depression, drowsiness, dysphagia, electrolyte imbalance, eosinophilia, eye discomfort, gout, gynaecomastia, hearing loss, hepatic disorders, hyperbilirubinaemia, hyperglycaemia, hypertension, hyperuricaemia, hypotension, increased risk of infection, laryngeal pain, lymphadenopathy, lymphopenia, malaise, memory loss, menstrual cycle irregularities, nerve disorders, oral disorders, palpitations, pancreatitis, peripheral coldness, pulmonary oedema, Raynaud's phenomenon, renal impairment, renal pain, respiratory disorders, restless legs, scrotal oedema, sepsis, sexual dysfunction, syncope, thrombocytosis, tinnitus, tremor, urinary frequency increased, vertigo. Rare or very rare: Angina pectoris, angioedema, arthritis, cardiac arrest, cataract, confusion, glaucoma, haemolytic anaemia, haemorrhagic ovarian cyst, hepatic failure (including fatal cases), hypersensitivity vasculitis, inflammatory bowel disease, intracranial pressure increased, muscle weakness, MI, myopathy, nail discolouration, pericardial disorders, pulmonary hypertension, seizure, SCARs, tumour lysis syndrome. Frequency not known: Embolism and thrombosis, hepatitis B reactivation, neoplasm complications, osteonecrosis, pericarditis

Interaction with other medicinal products and other forms of interaction

- Increased concentration of imatinib:
  - Antifungals: ketoconazole, fluconazole
  - Antiarrythmics: Amiodarone
  - CCBs: diltiazem, verapamil
  - Ciclosporin
  - Grapefruit
  - Protease Inhibitors
  - Macrolides: clarithromycin, erythromycin
- Decreased concentration of imatinib:
  - Antiepileptics: carbamazepine, phenytoin, phenobarbitone
  - Efavirenz, Nevirapine
  - Rifampicin
  - St Johns wort (*Hypericum perforatum*)
- Imatinib increases plasma concentrations of: Tamsulosin, Bedaquiline, amlodipine, nifedipine, cyclosporin, methylprednisolone, bromocriptine, methadone, sildenafil, atorvastatin, warfarin
- Increased risk of hepatotoxicity with paracetamol
- Increased risk of bleeding events with warfarin

Notes:

- Imatinib is a tyrosine kinase inhibitor
- Risk of HBV reactivation with BCR-ABL tyrosine kinase inhibitors An EU wide review has concluded that imatinib can cause hepatitis B reactivation, the MHRA recommends establishing HBV status in all patients before initiation of treatment
- Monitoring requirements: monitor for GI haemorrhage. Monitor CBCs regularly. Monitor

for fluid retention. Monitor liver function. Monitor growth in children (may cause growth retardation). Directions for administration: tablets may be dispersed in water or apple juice. Patient and Caregiver advice: patients or Caregivers should be given advice on how to administer imatinib tablets

Nilotinib

ATC code: L01EA03

Capsule, 200 mg, LOU 5

Indications and dose

Adult

Imatinib-resistant chronic myeloid leukaemia, oral: 300 mg twice daily in newly diagnosed patients with CML in the chronic phase, 400 mg twice daily in patients with chronic or accelerated phase CML with resistance or intolerance to prior therapy

Paediatric

Imatinib-resistant chronic myeloid leukaemia, oral:

Child below 2 years: There is no experience with treatment of patients in this age group.

Child over 2 years: 230 mg/m2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg)

Contraindications: Pregnancy

Precautions:

- Myesuppression: Reduce the dose or withhold nilotinib temporarily
- QT prolongation: Close monitoring for an effect on the QTc interval is advisable and a baseline ECG is recommended prior to initiating nilotinib therapy and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to nilotinib administration and should be monitored periodically during therapy.
- Patients should be tested for HBV infection before initiating treatment with nilotinib.

Pregnancy: Nilotinib should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breastfeeding: Women should not breastfeed during treatment and for at least 15 days after stopping treatment with nilotinib.

Adverse effects: low platelets, low WBCs, anemia, rashes, vomiting, diarrhea, and joint pains, QT prolongation, sudden death, pancreatitis, and liver problems.

Interactions: Refer to Imatinib above

Osimertinib

ATC code: L01EB04

Tablet, 80 mg, LOU 5

Indications and dose

Adult

Non-small cell lung cancer, adenocarcinoma, EGFR mutation positive:Oral,80mg once daily until disease progression or unacceptable toxicity.

Dosage modifications for toxicity:

- Pulmonary toxicity: Pneumonitis or interstitial lung disease; permanently discontinue treatment.
- Blood and bone marrow toxicity: Aplastic anaemia permanently discontinue treatment.
- Cutaneous toxicity: Steven-Johnson syndrome; permanently discontinue treatment.
- Cardiotoxicity: QTc interval> 500milliseconds on at least two separate ECGs; withhold treatment until QTc interval<481 milliseconds or to baseline then resume at reduced dose of 40 mg once daily.

QTc interval prolongation with signs and symptoms of life-threatening arrhythmia; permanently discontinue treatment.

- Other toxicities: Grade 3 or higher adverse reaction; withhold treatment for 3 weeks. If improvement to grade 0-2 may resume treatment at 80 mg or 40 mg once daily. If no improvement to grade 0-2 in 3 weeks; permanently discontinue treatment.

Paediatric

Safety and efficacy in children or adolescents less than 18 years has not been established.

Contraindications: Hypersensitivity to the active substance or any of the excipients.

Precautions: Interstitial lung disease, Steven-Johnson syndrome, QTc interval prolongation, aplastic anaemia, and ocular toxicity.

Hepatic impairment:

Mild to moderate liver impairment (Child-Pugh class A or B): No dose adjustments required.

Severe hepatic impairment (Child-Pugh class C): Use not recommended.

Renal impairment:

- Creatinine clearance >15 mL/min: No dosage adjustment is necessary.
- Creatinine clearance ≤15 mL/min: No recommended dose; use with caution.

Pregnancy: Should not be used during pregnancy. Women of childbearing age should use effective contraception during treatment and for 6 weeks following the last dose

Breastfeeding: Breast-feeding should be discontinued during treatment and for at least 2 weeks after the final dose.

Adverse effects: Diarrhoea, stomatitis, rash, stomatitis,

paronychia, pruritus, thrombocytopenia, lymphopenia, neutropenia, fatigue hypoglycaemia, eye disorders, decreased appetite, left ventricular ejection fraction, decreased, serum creatinine increased and cough.

Interactions with other medicines (*indicates serious):

- *Strong CYP3A inducers - examples: Phenytoin, rifampicin, carbamazepine and St John's Wort - concomitant use should be avoided.
- *Moderate CYP3A4 inducers - examples: bosentan, efavirenz, etravirine, modafinil- may also decrease osimertinib exposure and should be used with caution or avoided when possible.

Notes:

- The tablet should be swallowed whole with water, and it should not be crushed, split or chewed.
- If administration via nasogastric tube is required it should first be dispersed in 50 mL of non-carbonated water whole, then 15 mL administered for the residue rinses.

Palbociclib

ATC code: L01EF01

Tablet, 75 mg,125mg,100mg, LOU 5

Indications and dose

Adult

- *Breast cancer, advanced, initial endocrine based therapy: Oral*,125 mg once daily for 21 days followed by 7 days off to be repeated every 28 days in combination with aromatase inhibitor. Continue until disease progression or unacceptable toxicity.
- *Breast cancer, advanced, disease progression following endocrine based therapy: Oral*,125 mg once daily for 21 days followed by 7 days off to be repeated every 28 days in combination with fulvestrant. Continue until disease progression or unacceptable toxicity.

Dosage modifications for toxicity:

- Haematological toxicity:

Grade 1 or 2: No dose adjustment required.

Grade 3:

- Day 1 of cycle: Withhold dose, repeat blood counts within 1 week; when recovered to grade ≤2, start next cycle at same dose.
- Day 15 of first 2 cycles: If grade 3 on Day 15, continue at current dose to complete cycle; repeat blood counts on Day 22; if grade 4 on Day 22, see grade 4 dose modifications below.
- Prolonged (>1 week) recovery from grade 3 or recurrent grade 3 neutropenia in subsequent cycles: Consider dose reduction.

Grade 3 neutropenia and fever ≥38.5°C and/or infection and grade 4 haematological toxicity at any time: Withhold drug until recovery to grade ≤2 resume at next lower dose (see table below).

- Non haematological toxicity:

Grade 1 or 2: No dose adjustment required.

Grade ≥3 (if persisting despite medical treatment): Withhold until symptoms resolve to grade ≤1 or grade ≤2 can resume at the next lower dose (see table below).

Dose reduction level	Dose
Recommended dose	125mg
First dose reduction	100mg
Second dose reduction	75mg
Third dose reduction	Discontinue treatment

Paediatric: The safety and efficacy has not been established in paediatric patients.

Contraindications: Hypersensitivity to the active substance or any of the excipients.

Precautions:

- Bone marrow suppression: Neutropenia observed predisposing patients to infections.
- Interstitial lung disease /Pneumonitis- Patients should be monitored for pulmonary symptoms and treatment permanently discontinued for those who develop symptoms.

Hepatic impairment:

- Mild or moderate (Child-Pugh A or B): No dose adjustment required.
- Severe (Child-Pugh C): Reduce dose to 75 mg once daily, for 21 days, followed by 7 days off, repeat every 28 days.

Renal impairment: No dosage adjustment needed.

Pregnancy: Should not be used during pregnancy. Women of childbearing age should use effective contraception during treatment and for 3 weeks following the last dose males with female partners should use effective contraception during treatment and for 14 weeks following the last dose.

Breastfeeding: Use not recommended during breastfeeding and patients should not breastfeed during treatment and for 3 weeks following the last dose.

Adverse effects: Neutropenia, leukopenia, fatigue, elevated liver transaminases, stomatitis, decreased appetite, dysgeusia, venous thromboembolism, pneumonitis, diarrhoea, dry skin, rash, increased lacrimation, and blurred vision.

Interactions with other medicines (*indicates serious):

- Strong CYP3A4 inhibitors* (examples: ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, cobicistat, voriconazole and posaconazole) concurrent use should be avoided.
- Strong CYP3A inducers*(examples: carbamazepine, enzalutamide phenytoin, rifampicin and St John's Wort) concurrent use should be avoided.

Notes:

- Pre and peri menopausal women should have a luteinizing hormone releasing hormone (LHRH) agonist as part of their treatment combination.

» Tablets can be taken with or without food and should be taken whole with water and not broken or crushed.

» Tablets should not be taken with grapefruit or grapefruit juice.

Pazopanib

ATC code: L01EX03

Tablet, 200mg,400mg, LOU 5

Indications and dose

Adult

» *Renal cell carcinoma: oral,* 800 mg once daily, until disease progression or unacceptable toxicity.

» *Metastatic advanced soft tissue sarcoma: oral,* 800mg once daily until disease progression or unacceptable toxicity.

Dosage modifications for toxicity:

» Hepatic toxicity: For isolated ALT elevations 3-8 times Upper Limit Normal (ULN) continue and monitor weekly for 8 weeks if >8 times hold treatment until improvement to grade 1 then reintroduce at a reduced dose of 400 mg. Permanently discontinue if ALT elevations >3 times ULN despite dose reduction and for transaminase elevations >3 x ULN concurrently with bilirubin elevations >2 x ULN.

» Hypertension: Grade 2 or 3: initiate or adjust antihypertensive therapy and reduce dose (see table below). Grade 3 recurs despite dose reduction(s) and adjustment of antihypertensive therapy, Grade 4 or hypertensive crisis; permanently discontinue treatment.

» Haemorrhagic events: Grade 2 toxicity first occurrence; withhold treatment until improvement to ≤ grade 1 then resume at reduced dose (see table below) second occurrence and grade 3 and 4 toxicity regardless of occurrence permanently discontinue treatment.

» Thrombosis: venous thrombotic events grade 3; withhold treatment and resume same dose if managed appropriately for at least 1 week. Permanently discontinue treatment for grade 4 venous thrombotic and arterial thrombotic events of any grade.

Dose reduction level	Renal cell carcinoma	Soft tissue sarcoma
Initial dose	800 mg once daily	800 mg once daily
First reduction	400 mg once daily	600 mg once daily
Second reduction	200mg once daily	400 mg once daily
Third reduction	Discontinue treatment	Discontinue treatment

Paediatric: The safety and efficacy has not been established in children less than 18 years of age.

Contraindications: Hypersensitivity to the active substance or any of the excipients.

Precautions:

» Cardiac dysfunction: congestive heart failure and decreased LVEF have occurred, monitoring needed. Permanently discontinue treatment for severe dysfunction.

» Gastrointestinal (GI) perforations and fistula: Fatal perforation events have occurred. Permanent discontinuation of treatment for GI perforations and grade 4 fistula.

» Impaired wound healing: Treatment should be stopped at least 7 days prior to scheduled surgery and not administered for at least 2 weeks following a major surgery.

» Hypothyroidism: Periodic monitoring of thyroid function should be done, and hypothyroidism managed appropriately.

» Proteinuria: and withheld in proteinuria ≥3g per 24 hours until recovery. Therapy should be permanently discontinued in patients who do not improve or recur despite dose reductions or those who develop nephrotic syndrome.

» Posterior reversible encephalopathy syndrome (PRES): has been reported presents with visual and neurological disturbances. Treatment should be permanently discontinued.

» Interstitial lung disease /Pneumonitis- Patients should be monitored for pulmonary symptoms and treatment permanently discontinued for those who develop symptoms.

Hepatic impairment:

» Mild (bilirubin <1.5x ULN and any ALT): No dosage adjustment necessary.

» Moderate (bilirubin ≥1.5-3x ULN and any ALT): Reduce dose to 200 mg once daily.

» Severe (bilirubin >3x ULN and any ALT): Not recommended.

Renal impairment: No dosage adjustment required.

Pregnancy: Should not be used during pregnancy. Women of childbearing age should use effective contraception during treatment and for 2 weeks following the last dose males with female partners should use effective contraception during treatment and for 2 weeks following the last dose.

Breastfeeding: Use not recommended during breastfeeding and patients should not breastfeed during treatment and for 2 weeks following the last dose.

Adverse effects: diarrhoea, hair colour change, skin hyperpigmentation, palmar plantar erythrodysesthesia, exfoliative rash, hypertension, nausea, headache, fatigue, anorexia, vomiting, dysgeusia, stomatitis, infections, myelosuppression, hypothyroidism, hypertension, blurred vision, pain, elevated alanine aminotransferase and elevated aspartate aminotransferase.

Interactions with other medicines (*indicates serious):

» Strong CYP3A4 inhibitors* (examples: ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, cobicistat,

voriconazole and posaconazole) concurrent use should be avoided. If a strong CYP3A4 inhibitor must be used, reduce the pazopanib dose to 400 mg.

Irinotecan*, simvastatin, omeprazole* and antacids*

Notes:

- Tablet should be administered at least 1 hour before or 2 hours after a meal and should be taken whole with water and not broken or crushed.
- Tablet be administered at least 1 hour before or 2 hours after administration of short-acting antacids.

Rituximab

ATC code: L01XC02

Injection (IV), 10 mg/mL (10-mL vial), LOU 6

Injection (IV), 10 mg/mL (50-mL vial), LOU 6

Indications and dose

Adult

Non-Hodgkin's lymphoma (specialist use only) and chronic lymphocytic leukaemia (specialist use only), by IV infusion: Consult product literature

Paediatric: Not licensed for use in children

Contraindications: Severe infection, when used for granulomatosis with polyangiitis and microscopic polyangiitis, pemphigus vulgaris, or rheumatoid arthritis Severe heart failure, severe, uncontrolled heart disease

Precautions: History of cardiovascular disease, exacerbation of angina, arrhythmia, and heart failure have been reported, patients receiving cardiotoxic chemotherapy, exacerbation of angina, arrhythmia, and heart failure have been reported, pre-medication recommended to minimize adverse reactions (consult product literature). Predisposition to infection, transient hypotension occurs frequently during infusion (antihypertensives may need to be withheld for 12 hours before infusion).

When used for granulomatosis with polyangiitis and microscopic polyangiitis, or pemphigus vulgaris Pneumocystis jirovecii pneumonia—consult product literature for prophylaxis requirements

Adverse effects:

Common or very common: Angioedema, anxiety, appetite decreased, arrhythmias, bone marrow disorders, bursitis, cancer pain, cardiac disorder, chest pain, chills, dizziness, dysphagia, dyspnoea, ear pain, electrolyte imbalance, GI discomfort, GI disorders, hepatitis B, hypercholesterolaemia, hyperglycaemia, hyperhidrosis, hypertension, hypotension, insomnia, lacrimation disorder, malaise, migraine, multi organ failure, muscle complaints, muscle tone increased, nausea, nerve disorders, oedema, oral disorders, osteoarthritis, respiratory disorders, sensation abnormal, sepsis, skin reactions, throat irritation, tinnitus, vasodilation, weight decreased. Uncommon: Asthma, coagulation disorder, heart failure, hypoxia, ischaemic heart disease, lymphadenopathy, taste altered. Rare or very rare: Cytokine release syndrome, facial paralysis, renal failure, SJS (discontinue), toxic epidermal necrolysis (discontinue), tumour lysis syndrome, vasculitis, vision disorders. Frequency not known: Epistaxis, hearing loss, hypogammaglobulinaemia, infective thrombosis, influenza like illness, irritability, muscle weakness, nasal congestion, posterior reversible encephalopathy syndrome, psychiatric disorder, seizure, skin papilloma, tremor

Interactions with other medicines: → monoclonal antibodies. Not significant

Notes: Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking rituximab. Patients with positive hepatitis B serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation, treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for up to a year following the last infusion (consult product literature).

Sorafenib

ATC code: L01EX02

Tablet, 200mg, LOU 5

Indications and dose

Adult

- *Hepatocellular carcinoma (HCC):* Oral, 400mg twice daily until disease progression or unacceptable toxicity.
- Renal cell carcinoma (RCC): *Oral,* 400mg twice daily until disease progression or unacceptable toxicity.
- Thyroid carcinoma - differentiated: *Oral,* 400mg twice daily until disease progression or unacceptable toxicity.

Dosage modifications for toxicity:

Cardiac toxicity: Grade 3 heart failure interrupt treatment until resolves to grade ≤1 then resume dose reduced by one dose level (see table below). Permanently discontinue treatment for grade 4 heart failure and cardiac infarction of grade 2 or higher.

Hypertension: Grade 2 or 3: initiate or adjust antihypertensive therapy and reduce dose (see table below). Grade 4 toxicity, permanently discontinue treatment.

Haemorrhagic events: Grade 2 or higher requiring medical intervention permanently discontinue treatment.

Dermatological toxicity: Grade 2 toxicity first occurrence continue with same dose for HCC and RCC and dose reduce for thyroid carcinoma (see table below).If no improvement within 7 days or second or third occurrence interrupt treatment and dose reduce by one dose level (see table below) when resuming treatment. Discontinue treatment for fourth occurrence. Grade 3 toxicity first and second occurrence interrupt treatment until resolved to ≤ grade 1 and decrease dose by one dose level when

resuming treatment, for third occurrence permanently discontinue treatment.

Hepatotoxicity: If ALT, AST >3 times upper limit normal (ULN) with bilirubin > 2 times ULN; permanently discontinue treatment.

Dose reduction level	Renal cell carcinoma and Hepatocellular carcinoma	Differentiated t hyroid carcinoma
Initial dose	400 mg twice daily	400 mg twice daily
First reduction	400 mg once daily	400 mg (morning) and 200 mg (evening) 12 hours apart
Second reduction	200 mg once daily	200 mg twice daily
Third reduction	Discontinue treatment	200 mg once daily

Paediatric: The safety and efficacy has not been established in children.

Contraindications: Hypersensitivity to the active substance or any of the excipients.

Precautions: QT interval prolongation, Gastrointestinal perforation, Aneurysms and artery dissections, hypoglycaemia, wound healing complications

Hepatic impairment: (At baseline)**:**

- Mild or moderate (Child-Pugh A or B): No dose adjustment required.
- Severe (Child-Pugh C): No dose adjustment required, use with caution.

Renal impairment: No dose adjustment required.

Pregnancy: Should not be used during pregnancy. Women of childbearing age should use effective contraception during treatment and for 6 months following the last dose males with female partners should use effective contraception during treatment and for 3 months following the last dose.

Breastfeeding: Use not recommended during breastfeeding and patients should not breastfeed during treatment and for 2 weeks following the last dose.

Adverse effects: diarrhoea, stomatitis, fatigue, alopecia, infection, palmar plantar erythrodysesthesia syndrome, leukopenia, neutropenia, anaemia, thrombocytopenia, hypothyroidism, hypocalcaemia, hypokalaemia hyponatraemia, hypoglycaemia, peripheral sensory neuropathy, dysgeusia congestive heart failure, myocardial infarction, myalgia, renal failure and proteinuria

Interactions with other medicines (*indicates serious): Irinotecan*, paclitaxel*, carboplatin, enzalutamide*, clarithromycin, Carbamazepine, mirtazapine, phenobarbital*, phenytoin*, lopinavir*, itraconazole*, ketoconazole*, voriconazole* and warfarin.

Notes:

- Tablet should be administered on an empty stomach at least 1 hour before or 2 hours after a meal.
- Tablet should be administered at least 1 hour before or 2 hours after a meal and should be taken whole with water and not broken or crushed.

Trastuzumab

ATC code: L01XC03

Powder for injection, 150-mg vial, 440 mg vial + diluent LOU5

Solution for subcutaneous injection, 600-mg vial, LOU 5

Indications and dose

Early stage and metastatic HER2-positive breast cancer, gastric cancer

- *Three-week schedule: intravenous,* Initial loading dose of 8 mg/kg body weight and maintenance dose at three-week intervals of 6 mg/kg body weight, beginning three weeks after the loading dose.
- *Weekly schedule: intravenous,* Initial loading dose of 4 mg/kg body weight and a weekly maintenance dose of 2 mg/kg body weight, beginning one week after the loading dose.

Early stage and metastatic HER2-positive breast cancer: subcutaneous, 600mg once every 3 weeks.

- *Duration of treatment*
- Patients with metastatic breast cancer or metastatic gastric cancer to be treated until progression of disease.
- Patients with early breast cancer to be treated for 1 year or until disease recurrence, whichever occurs first; extending treatment in early breast cancer beyond 1 year is not recommended.

Contraindications: Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients. Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

Pregnancy: If a pregnant woman is treated with trastuzumab, or if a patient becomes pregnant while receiving trastuzumab or within 7 months following the last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable.

Breastfeeding: Women should not breastfeed during trastuzumab therapy and for 7 months after the last dose.

Adverse effects: Neutropenia, Leukopenia, Anaemia, Lymphopenia, Thrombocytopenia, infections, nasopharyngitis, weight loss, anorexia, insomnia, tremor, dizziness, headache

Interactions with other medicines Immunoglobulins: Not significant.

Notes: Method of administration:

- Intravenous : loading dose should be administered as a 90-minute IV infusion. Do not administer as an IV push or bolus.
- Subcutaneous:Administered over 2-5 minutes alternating between the left and right thigh. New injections to be administered on healthy skin at least 2.5cm from the previous.

9.2.3. Immunomodulators

Filgrastim

ATC code: L03AA02

Injection (prefilled syringe), 120 micrograms/0.2 mL, 300 micrograms/0.5 mL, LOU 5

Indications and dose

Use as primary prophylaxis in those at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy; use as secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy, to facilitate administration of dose-dense chemotherapy regimens

Adult and paediatric

5 micrograms/kg/day SC or IV infusion (short 15–30 min or continuous); may increase by 5 micrograms/kg increments according to duration and severity of absolute neutrophil count (ANC)

Do not administer within the 24-hour period prior to chemotherapy.

Contraindications: History of serious allergic reactions to filgrastim or pegfilgrastim products

Precautions: In case of pulmonary adverse effects, discontinue filgrastim and initiate appropriate treatment. Urinalysis monitoring is recommended.

Pregnancy: Filgrastim is not recommended during pregnancy.

Breastfeeding: A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from filgrastim therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Adverse effects: mild bone pain after repeated administration, and local skin reactions at the site of injection, serious allergic reactions (including a rash over the whole body, shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, and sweating), ruptured spleen (sometimes resulting in death), alveolar hemorrhage, acute respiratory distress syndrome, hemoptysis, Severe sickle cell crises

Interactions with other medicines: Not significant.

Lenalidomide

ATC code: L04AX04

Capsule, 5 mg, 25 mg, LOU 5

Indications and dose

Adult

In combination with dexamethasone for treatment of multiple myeloma (MM), oral: 25 mg daily on days 1–21 of repeated 28-day cycles. *Ineligible for autologous hematopoietic stem cell transplantation (auto-HSCT):* Continue until disease progression or unacceptable toxicity

Dexamethasone schedule

40 mg PO daily on days 1–4, 9–12, and 17–20 of each 28-day cycle for first 4 cycles, then 40 mg PO daily on days 1–4 every 28 days

Age >75 yr: 20 mg PO daily on days 1, 8, 15, and 22 of each 28-day cycle

Indicated as maintenance therapy for MM following auto-HSCT, oral: Initiate after adequate hematologic recovery (i.e., ANC ≥1000/mcL and/or platelet counts ≥75,000/mcL)

- Starting dose: 10 mg daily continuously (i.e., day 1–28 of repeated 28-day cycles) until disease progression or unacceptable toxicity
- After 3 cycles: May increase dose to 15 mg daily if tolerated

Hematopoietic stem cell mobilization should occur within 4 cycles of a lenalidomide-containing therapy.

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Women who are pregnant. Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met

Precautions: Risk of hematologic toxicity, can cause significant neutropenia and thrombocytopenia. Patients with known risk factors of MI – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidaemia). Use with caution in renal impairment. Increases risk of mortality in patients with CLL with monotherapy, therapy not indicated and not recommended in CLL outside of controlled clinical trials. Fatal instances of tumor lysis syndrome reported

Pregnancy: Avoid during pregnancy, if taken during pregnancy, likely to cause birth defects or foetal death

Breastfeeding: Discontinue breastfeeding during therapy

Adverse effects: diarrhea, itchiness, joins pain, fever, headache, trouble sleeping, low blood platelets, low WBCs, blood clots

Interaction with other medicinal products and other forms of interaction

- Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone
- Oral contraceptives: Effective measures to avoid pregnancy must be taken
- Warfarin: Close monitoring of warfarin concentration is advised during the treatment.
- Digoxin: Monitoring of the digoxin concentration is advised during lenalidomide treatment.
- Statins: There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Peg-Filgrastim

ATC code: L03AA13

Prefilled syringe, 6mg/0.6mL, LOU 5

Indications and dose

Adult

Prevention of chemotherapy-induced neutropenia: *Subcutaneous injection,* 6mg once per chemotherapy cycle at least 24 hours after completion of chemotherapy.

Acute hematopoietic radiation injury syndrome: *Subcutaneous injection,* 6mg once weekly for 2 doses.

Paediatric

Prevention of chemotherapy-induced neutropenia: subcutaneous injection; should be administered at least 24 hours after completion of chemotherapy.

- <10 kg: 0.1 mg/kg (0.01 mL/kg) SC once per chemotherapy cycle
- 10-20 kg: 1.5 mg (0.15 mL) SC once per chemotherapy cycle
- 21-30 kg: 2.5 mg (0.25 mL) SC once per chemotherapy cycle
- 31-44 kg: 4 mg (0.4 mL) SC once per chemotherapy cycle
- >45kg : 6 mg(0.6ml) SC once per chemotherapy cycle

Acute hematopoietic radiation injury syndrome: Subcutaneous injection; 2 doses administered 1 week apart

- <10 kg: 0.1 mg/kg (0.01 mL/kg)
- 10-20 kg: 1.5 mg (0.15 mL)
- 21-30 kg: 2.5 mg (0.25 mL)
- 31-44 kg: 4 mg (0.4 mL)
- >45kg: 6 mg(0.6ml)

Contraindications: Hypersensitivity to pegfilgrastim, filgrastim or excipients.

Precautions: Aortitis, capillary leak syndrome, leucocytosis, hypersensitivity, myelodysplastic syndrome, nephrotoxicity, splenic rupture, acute respiratory distress syndrome.

Hepatic impairment: No dose adjustments provided.

Renal impairment: No adjustments necessary.

Pregnancy: not recommended during pregnancy.

Breastfeeding: Use with caution.

Adverse effects: Bone pain, pain in extremities, leucocytosis, splenic rupture and splenomegaly, glomerulonephritis, thrombocytopenia, and cutaneous vasculitis.

Interactions with other medicines (*indicates serious): bleomycin, topotecan.

Notes:

- Allow prefilled syringes to reach room temperature for a minimum of 30 min before administration.
- Administer between 14 days before and 24 hr after administration of cytotoxic chemotherapy.

Pembrolizumab

ATC code: L01XC18

Injection, 100 mg/4 mL, LOU 6

Indications and dose

Adult

Unresectable or metastatic melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, metastatic small cell lung cancer, microsatellite instability-high cancer, gastric and cervical cancers, primary mediastinal large B-cell lymphoma, hepatocellular and Merkel cell carcinomas, urothelial and renal cell carcinomas, oesophageal and endometrial cancers, IV infusion

- Monotherapy: Either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an IV infusion over 30 minutes
- Part of combination therapy: 200 mg every 3 weeks administered as an IV infusion over 30 minutes

Contraindications: Hypersensitivity to the active substance or to any of the excipients

Adverse effects: pneumonia, anemia, thrombocytopenia, lymphopenia, neutropenia, infusion-related reaction, hypothyroidism, hyperthyroidism, thyroiditis, headache, decreased appetite, insomnia, dizziness, neuropathy peripheral, lethargy, dysgeusia, dyspnea, cough, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia

Interactions with other medicines:

The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions. Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

Thalidomide

ATC code: L04AX02

Capsule, 100 mg, LOU 5

Indications and dose

Adult

Untreated multiple myeloma, aged ≥65 years or ineligible for high-dose chemotherapy (in combination with melphalan and prednisolone), oral

Table: Starting doses for thalidomide in combination with melphalan and prednisolone

Age (years)	Absolute neutrophil count (/μL)		Platelet count (/μL)	Thalidomide	Melphalan (mg/kg daily)	Prednisolone (mg/kg/daily)
≤75	≥1,500	AND	≥100,000	200 mg daily	0.25	2
≤75	<1,500 but ≥1,000	OR	<100,000 but ≥50,000	200 mg daily	0.125	2
>75	≥1,500	AND	≥100,000	100 mg daily	0.20	2
>75	<1,500 but ≥1,000	OR	<100,000 but ≥50,000	100 mg daily	0.10	2

Dosing considerations:

- Thalidomide dosed once daily at bedtime on days 1 to 42 of each 42-day cycle. A maximum number of 12 cycles of 6 weeks (42 days) should be used.
- Because of the sedative effect associated with thalidomide, administration at bedtime is known to generally improve tolerability.
- Melphalan dosed once daily on days 1 to 4 of each 42-day cycle
- Melphalan dosing: Reduce by 50% for moderate (CrCl: ≥30 but <50 mL/min) or severe (CrCl: <30 mL/min) renal insufficiency
- Maximum daily melphalan dose: 24 mg (patient ≤75 years old) or 20 mg (patient >75 years old)
- Prednisolone dosed once daily on days 1 to 4 of each 42-day cycle

Contraindications: Hypersensitivity to thalidomide or to any of the excipients.

Male patients unable to follow or comply with the required contraceptive measures

Pregnancy: Thalidomide is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the Pregnancy Prevention Programme are met

Breastfeeding: breastfeeding should be discontinued during therapy with thalidomide

Adverse effects: Neutropenia, leukopenia, anaemia, lymphopenia, thrombocytopenia, confusional state, depression, peripheral neuropathy, tremor, dizziness, paraesthesia, dysaesthesia, somnolence

Interactions with other medicines:

- Caution should be used when thalidomide is given in combination with medicinal products that cause drowsiness.
- Due to thalidomide's potential to induce bradycardia, caution should be exercised with medicinal products having the same pharmacodynamic effect such as active substances known to induce torsade de pointes, beta blockers or anticholinesterase agents.
- Medicinal products known to be associated with peripheral neuropathy (e.g., vincristine and bortezomib) should be used with caution in patients receiving thalidomide.

9.2.4. Hormones and Antihormones

Abiraterone

ATC code: L02BX03

Tablet, 250 mg, LOU 5

Indications and dose

Metastatic castration-resistant prostate cancer, oral: 1,000 mg as a single daily dose that must not be taken with food; taking the tablets with food increases systemic exposure to abiraterone

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Women who are or may potentially be pregnant. Severe hepatic impairment [Child-Pugh Class C]

Pregnancy and breastfeeding: Abiraterone is not for use in women

Adverse effects: tiredness, vomiting, headache, joint pain, high blood pressure, swelling, low blood potassium, high blood sugar, hot flashes, diarrhea, and cough, liver failure, adrenocortical insufficiency.

Interactions with other medicines:

- Spironolactone: effects opposite to those of abiraterone
- Antiepileptics: carbamazepine, phenytoin, carbamazepine: decrease levels of abiraterone

Anastrozole

ATC code: L02BG03

Tablet, 1 mg, LOU 5

Indications and dose

Adult

Treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer, oral: 1 mg tablet taken once a day

Contraindications: Pregnant or breastfeeding women. Hypersensitivity to the active substance or to any of the excipients

Precautions: Anastrozole is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients. As Anastrozole lowers circulating estrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture. Anastrozole should not be used in premenopausal women.

Adverse effects: hot flashes, asthenia, arthritis, pain, arthralgia, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, headache, bone pain, peripheral edema, increased cough, dyspnea, pharyngitis and lymphedema.

Interactions with other medicines: Co-administration of tamoxifen or oestrogen-containing therapies with Anastrozole should be avoided as this may diminish its pharmacological action

Bicalutamide

ATC code: L02BB03

Tablet, 50 mg, LOU 5

Indications and dose

Adult

Adjuvant to radical prostatectomy or radiotherapy in patients with locally advanced prostate cancer at high risk for disease progression, oral: 150 mg tablet once a day

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Bicalutamide is contraindicated in children under the age of 18 years, and in females.

Co-administration of terfenadine, astemizole or cisapride with bicalutamide is contraindicated.

Adverse effects: rash, alopecia, hirsutism, asthenia, edema, weight gain

Notes: The tablets should be swallowed whole with liquid. Bicalutamide 150 mg tablets should be taken continuously for at least 2 years or until disease progression.

Dexamethasone

ATC code: H02AB02

Tablet, 500 micrograms, 4 mg scored LOU 5

Injection, 4 mg/1-mL amp (as sodium phosphate), LOU 5

Indications and dose

Adult and Child

Acute lymphoblastic leukaemia, multiple myeloma: Dosage must be individualized on the basis of the disease and the response of the patient. To minimize adverse effects, the lowest possible dosage adequate to control the disease process should be used.

Contraindications: Systemic fungal infection, systemic infection unless specific anti-infective therapy is employed, hypersensitivity to the active ingredient or any other component of this medication, administration of live virus vaccines

Adverse effects on prolonged use: thrush, bone loss, cataracts, easy bruising, or muscle weakness

Interactions: Check steroids.

Goserelin

ATC code: L02AE03

Implant (in syringe applicator), 3.6 mg (as acetate), 10.8 mg (as acetate), LOU 5

Indications and dose

Adult

Prostate cancer, advanced breast cancer, endometriosis, uterine fibroids, SC injection: One 3.6-mg depot injected subcutaneously into the anterior abdominal wall every 28 days

OR

One 10.8 mg depot injected subcutaneously into the anterior abdominal wall, every 3 months (12 weeks).

Women who are anaemic as a result of uterine fibroids, SC injection: 3.6 mg depot every 28 days with supplementary iron may be administered for up to

three months before surgery

Contraindications: Hypersensitivity to the active substance or to any of the excipients

Pregnancy and breastfeeding

Adverse effects: hot flush, hyperhidrosis, rash, bone pain, erectile dysfunction, vulvovaginal dryness, breast enlargement, gynecomastia.

Hydrocortisone

ATC code: H02AB09

Powder for injection, 100-mg vial (as sodium succinate), LOU 5

Indications and dose

Adult

Acute lymphoblastic leukaemia, multiple myeloma: Individualised based on the disease

Interactions: Check steroids.

Letrozole

ATC code: L02BG04

Tablets ,2.5 mg, LOU 5

Indications and dose

Adult

- Breast cancer, adjuvant therapy: *oral,*2.5mg once daily for 5-10 years.
- Breast cancer, advanced, first or second line therapy: *oral,*2.5mg once daily until disease progression.

Paediatric: Safety and effectiveness not established in paediatric patients.

Contraindications: Pregnancy, known hypersensitivity to letrozole

Precautions: Hypercholesterolemia, cirrhosis, severe hepatic impairment, and osteoporosis

Hepatic impairment: Reduce dose to 2.5 mg every other day in severe impairment (child-Pugh class C)

Renal impairment: Dose adjustment not necessary.

Pregnancy: Contraindicated in pregnancy.

Breastfeeding: Infant risk cannot be ruled out.

Adverse effects: Common oedema, sweating, hot flashes, arthralgia, increased fracture risk, hypercholesterolemia, and fatigue.

Interactions with other medicines (*indicates serious): ethinylestradiol*, tamoxifen*, methadone and nintedanib.

Notes:

- May take with or without food.
- Supplementation with calcium and vitamin D supplements is required for long term treatment.
- Ovarian function suppression should be given in combination for pre/perimenopausal patients.

Methylprednisolone

ATC code: H02AB04

Powder for injection, 500 mg (as sodium succinate) in vial, LOU 5

Indications and dose: *See section 9.1*

Interactions: Check steroids.

Octreotide

ATC code: H01CB02

Injection kit, 20mg, LOU 5.

Indications and dose

Adult

Carcinoid syndrome: Intramuscular, 20mg every 4 weeks.

Paediatric

Safety and efficacy not established.

Contraindications: Known hypersensitivity to the active substance or to any of the excipients

Precautions:

- Cardiovascular events: Cases of bradycardia have been reported.
- Hypothyroidism: suppresses TSH secretion, monitor for hypothyroidism.
- Glucose metabolism: Affects glucose regulation, with prolonged hyperglycaemia or hypoglycaemia.
- Depressed vitamin B12 levels with abnormal Schillings test.

Hepatic impairment: Patients with liver cirrhosis reduced initial dose of 10mg every 4weeks.

Renal impairment: No dose adjustment is necessary.

Pregnancy: Avoid use in pregnancy

Breastfeeding: Patients should not breast-feed during treatment

Adverse effects: cholelithiasis, hepatitis, glucose dysregulation, abdominal pain, nausea, flatulence, diarrhoea, headache, Pruritus, rash, alopecia, and bradycardia.

Interactions with other medicines: Beta blockers, calcium channel blockers, indapamide, cyclosporine, quinidine, disopyramide, ciclosporin, cimetidine, bromocriptine, and anti-diabetic drugs.

Notes:

- Kit should remain at room temperature for 30-60 min prior to preparation of the drug suspension.
- Repeat intramuscular injections should be alternated between the left and right gluteal muscle.

Prednisolone

Tablet, 5 mg, 20 mg, LOU 5

Oral liquid:, 15 mg/5 mL, LOU 5

Indications and dose

Adult

Leukaemias and lymphomas, oral: Initially up to 100 mg daily, then gradually reduce, if possible to 20–40 mg daily

Paediatric

Leukaemias and lymphomas, oral

Child up to 1 year: Initially up to 25 mg, then gradually reduced to 5–10 mg daily

Child 2–7 years: Initially up to 50 mg daily, then gradually reduced to 10–20 mg daily

Child 8–12 years: Initially up to 75 mg, then gradually reduced to 15–30 mg daily

Contraindications: untreated bacterial, viral, and fungal infections, avoid live virus vaccines.

Precautions: monitor body weight, blood pressure, fluid and electrolyte balance, and blood glucose concentration throughout treatment, adrenal suppression during and for some months after withdrawal (intercurrent infection or surgery may require increased dose of corticosteroid or temporary reintroduction if already withdrawn), quiescent amoebiasis, strongyloidiasis, or TB possibly reactivated, increased severity of

viral infections, particularly chickenpox and measles (passive immunization with immunoglobulin required), hypertension, recent MI, congestive heart failure, elderly, children and adolescents (growth retardation possibly reversible), renal impairment, hepatic impairment, diabetes mellitus, osteoporosis, glaucoma, corneal perforation, severe psychosis, epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy, pregnancy, and breastfeeding

Adverse effects: GI effects including dyspepsia, esophageal

ulceration, development of or aggravation of peptic ulcers, abdominal distension, acute pancreatitis, increased appetite and weight gain, adrenal suppression with high doses, leading to cushingoid symptoms (moon face, acne, bruising, abdominal striae, truncal obesity, muscle wasting), menstrual irregularities and amenorrhea, hypertension, osteoporosis, with resultant vertebral collapse and long-bone fractures, avascular osteonecrosis, ophthalmic effects including glaucoma, subcapsular cataracts, exacerbation of viral or fungal eye infections, diabetes mellitus, thromboembolism

Interactions: Check steroids.

Notes:

- Prednisolone is a representative corticosteroid with mainly glucocorticoid activity. Various drugs can serve as alternatives.
- Prednisolone is a complementary list medicine for the treatment of malignant neoplasms.

Tamoxifen

ATC code: L02BA01

Tablet, 20 mg (as citrate), LOU 5

Indications and dose

Adult

Adjuvant treatment of estrogen-receptor-positive breast cancer, metastatic breast cancer, oral: 20 mg daily

Contraindications: Pregnancy. Pre-menopausal patients must be carefully examined before treatment for all indications to exclude the possibility of pregnancy. Hypersensitivity to the active substance or to any of the excipients.

Concurrent anastrozole therapy. Patients with a personal or family history of confirmed idiopatic venous thromboembolic events or a known genetic defect.

Women with a history of deep vein thrombosis or pulmonary embolus.

Women who require concomitant coumarin-type anticoagulant therapy

Adverse effects: hot flushes, endometrial changes (symptoms such as vaginal bleeding and other menstrual irregularities, vaginal discharge, pelvic pain require immediate investigation), increased pain and hypercalcaemia with bony metastases, tumour flare, nausea and vomiting, liver enzyme changes (rarely cholestasis, hepatitis, hepatic necrosis), hypertriglyceridemia (sometimes with pancreatitis), thromboembolic events, decreased platelet count, oedema, alopecia, rash, headache, visual disturbances including corneal changes, cataracts, retinopathy, rarely interstitial pneumonitis, and hypersensitivity reactions including angioedema, SJS, and bullous pemphigoid.

Interactions with other medicines:

- Tamoxifen increases anticoagulant effect of coumarins
- Rifampicin increases exposure to tamoxifen
- Terbinafine decreases efficacy of tamoxifen
- Increased risk of thromboembolism on concurrent use with: Blemycin, cyclophosphamide, doxorubicin, fluorouracil, methotrexate, tranexamic acid, vincristine.

9.2.5. Supportive Medicines

Allopurinol

ATC code: M04AA01

Tablet, 100 mg, 300 mg, LOU 5

Indications and dose

Adult

Prevention and treatment of antineoplastic induced hyperuricemia and tumour lysis syndrome, oral: 600 – 800mg divided in divided doses every 8 to 12 hours starting one to two days before chemotherapy for malignancies with high risk of tumour lysis syndrome following treatment. If dosage on a mg/kg body weight basis is required, 2 to 10 mg/kg body weight/day should be used. **Note: Minimum dose: 100 – 200mg**

Paediatric

Prevention and treatment of antineoplastic induced hyperuricemia and tumour lysis syndrome, oral:

Child below 15 years: 10 to 20mg/kg bodyweight/day up to a maximum of 400mg daily starting 1 to 2 days before chemotherapy for malignancies with high risk of tumour lysis syndrome following treatment

Contraindications: Hypersensitivity to allopurinol

Precautions: Discontinue at first sign of allergic reactions (first sign of rash, vasculitis, or SJS, drug rash with eosinophilia and systemic symptoms and/or generalized vasculitis, irreversible hepatotoxicity)

Adverse effects: skin reactions, hepatic dysfunction, angioedema, fever

Interactions:

Increased risk of haematological toxicity when given with azathioprine, mercaptopurine

Increased risk of hypersensitivity and haematological reactions with ACEIs

Increased risk of skin rash with penicillins

Increased risk of hypersensitivity reactions with thiazides

Increased risk of hyperuricemia with pyrazinamide.

Febuxostat

ATC code: MA4AA03

Tablet 40 mg, LOU 5

Indications and dose

Adult

Tumour lysis syndrome, prevention, oral: initially 40 mg once daily or 120 mg once daily starting 1-2 days before start of chemotherapy for 14 days until normalization of laboratory evidence of tumour lysis.

Paediatric: Safety and efficacy not established

For Contraindications, Precautions, use in Hepatic and Renal impairment, Pregnancy, Breastfeeding, Adverse effects, Interactions with other medicines and notes, *See: Febuxostat in section 28.1*

Magnesium Sulphate

ATC code: A12CC02

Injection, 4% in 100mL vial, LOU 5

Indications and dose

Adult

Prevention of cisplatin induced nephrotoxicity, IV Infusion:20meq (2.5g) over 3 hours before cisplatin administration.

Paediatric

Specialist advise.

For Contraindications, Precautions, use in Hepatic and Renal impairment, Pregnancy, Breastfeeding, Adverse effects, Interactions with other medicines and notes, *See: In section 6*

Notes:

» For prevention of cisplatin induced nephrotoxicity should be diluted in 1000ml of normal saline and infused over 3 hours

Mannitol

ATC code: B05BC01

Injectable solution, 20%, LOU 5

Indications and dose

Adult

Forced diuresis in prevention of cisplatin induced nephrotoxicity: Intravenous infusion, 12.5g-20g prior to cisplatin dose.

Paediatric

Assessment of renal function, test dose (to assess adequate renal function), by IV infusion

Child all ages: 200 mg/kg (maximum dose 12.5 g) given over 3 to 5 minutes to produce urine flow of at least 1 mL/kg/hour for 1–3 hours.

For Contraindications, Precautions, use in Hepatic and Renal impairment, Pregnancy, Breastfeeding, Adverse effects, and Interactions with other medicines, *See: Mannitol in section 18.*

Notes:

» Solutions containing more than mannitol 15% may crystallize during storage, crystals must be redissolved by warming solution before use and solution must not be used if any crystals remain, IV administration sets must have a filter, mannitol should not be administered with whole blood or passed through the same transfusion set as blood.

» Use of mannitol for forced diuresis in prevention of cisplatin induced nephrotoxicity should be considered mainly for patients receiving high dose cisplatin>100mg/m2 or with pre-existing hypertension.

Mesna

ATC code: V03AF01

Injection, 100 mg/mL (2-mL amp, 4-mL amp), LOU 5

Indications and dose

Adult and Paediatric

Prevention of urothelial toxicity, including haemorrhagic cystitis, microhaematuria, and macrohaematuria in patients treated with ifosfamide and cyclophosphamide, in doses considered to be urotoxic.

When ifosfamide or cyclophosphamide is used as an IV bolus: IV injection over 15–30 minutes at 20% of the simultaneously administered oxazaphosphorine on a weight-for-weight basis (w/w). The same dose of mesna is repeated after 4 and 8 hours. The total dose of mesna is 60% (w/w) of the oxazaphosphorine dose. This is repeated on each occasion that cytotoxic agents are used.

When Ifosfamide is given as a 24-hour infusion, Mesna can be used as concurrent infusion with an initial 20% (w/w) of total ifosfamide dose given as iv bolus mesna dose then an infusion at 100% (w/w) of the ifosfamide dose over 24 hours followed by a further 12-hour infusion of 60% (w/w) of the ifosfamide dose. (Total mesna dose being 180% (w/w) of ifosfamide dose.

Contraindications: Hypersensitivity to mesna or

other thiol compounds

Precautions: Does NOT prevent nephrotoxicity, myelosuppression, or neurotoxicity

Contains benzyl alcohol as preservative (associated with potentially fatal "Gasping Syndrome" in preemies)

Will not prevent haemorrhagic cystitis in all patients, examine morning urine specimen for hematuria prior to ifosfamide or cyclophosphamide treatment.

Does not prevent or improve other toxicities associated with ifosfamide or cyclophosphamide.

If patient vomits within 2 hours after PO dose, repeat dose or give IV.

Mesna does not prevent thrombocytopenia-related haematuria.

Injection contains preservative benzyl alcohol which has been associated with serious adverse reactions and death when administered intravenously to premature neonates and low birth weight infants, avoid use.

Adverse effects: lymphadenopathy, decreased appetite, dehydration, headache, light-headedness, drowsiness, dizziness, flushing.

Notes:

- Multiple protocols exist; Check specific chemotherapy regimen and institutional guidelines where available.
- Mesna can be mixed in the same infusion bag as ifosfamide or cyclophosphamide.
- Contents of Mesna ampoule may be mixed with a flavoured soft drink e.g., orange juice or cola and taken orally.
- Oral dose of Mesna should be 40% (w/w) of ifosfamide or cyclophosphamide administered 2hours before, 2 hours and 6 hours after ifosfamide or cyclophosphamide.

Rasburicase

ATC code: V03AF07

Injection, 7.5 mg/vial, LOU 5

Indications and dose

Adult

Management of tumor lysis syndrome, IV infusion: 0.20 mg/kg/day, administered as a once daily 30-minute IV infusion in 50 mL of a sodium chloride 9 mg/mL (0.9%) solution

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia.

Precautions: Screen patients for G6PD deficiency, immediately and permanently discontinue therapy in any patient developing hemolysis, institute appropriate patient monitoring and support measures (e.g., transfusion support)

Patients should receive adequate hydration as part of uric acid management

Safety and efficacy beyond 5 day or >1 course unknown

Efficacy may be reduced with subsequent courses of therapy due to its immunogenic characteristics, can elicit and antibody response

Immediately and permanently discontinue therapy in any patient identified as having developed methaemoglobinemia, institute appropriate monitoring and support measures (e.g., transfusion support, methylene-blue administration)

Interferes with serum uric acid measurement unless blood sample chilled immediately and assayed within 4 hour

Discontinue therapy in any patient developing clinical evidence of a serious hypersensitivity reaction

Adverse effects: anaphylaxis, methaemoglobinemia, nausea, vomiting, abdominal pain, rash, headache, mucositis, neutropenia, sepsis

Sodium Hydrogen Carbonate (Sodium Bicarbonate)

ATC code: B05XA02

Injectable solution, 8.4% in 10 mL amp (equivalent to Na+ 1000 mmol/L, HCO3- 1000 mmol/L), LOU 5

Indications and dose

Adult

Urinary alkalinization: Intravenous infusion, 50-100 milliequivalents, repeat as needed to achieve urinary PH of 7.5-to 8.5.

Paediatric

Specialists advise for urinary alkalinization in oncology.

For Contraindications, Precautions, use in Hepatic and Renal impairment, Pregnancy, Breastfeeding, Adverse effects, Interactions with other medicines and notes, *See: section 31.*

Zoledronic Acid

ATC code: M05BA08

Injection (Concentrate solution for infusion), 800 micrograms/mL (5-mL vial), LOU 5

Indications and dose

Adult

Hypercalcaemia of malignancy, Multiple Myeloma, Bone Metastasis from solid tumours, IV Infusion (over 15minutes or more): 4mg every 3 to 4 weeks

Dose modification:

Renal Impairment

- CrCl > 60mL/min: 4mg
- CrCl 50- 60mL/min: 3.5mg
- CrCl 40 - 49mL/min: 3.3mg
- CrCl 30 - 39mL/min: 3mg

CrCl <30mL/min: Not Recommended

If renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value.

Paediatric

Safety and efficacy in Malignancy not established.

Contraindications: Hypersensitivity to the active substance, to any bisphosphonates or to any of the excipients. Patients with hypocalcaemia. Severe renal impairment with CrCl < 35 mL/min. Pregnancy and breastfeeding.

Precautions: Atypical femoral fractures. cardiac disease (avoid fluid overload), concomitant medicines that affect renal function.

Hepatic impairment: Dose adjustment not necessary, caution in severe hepatic impairment.

Renal impairment: Avoid in tumour-induced hypercalcaemia if serum creatinine above 400 micromol/L. Avoid in advanced malignancies involving bone if eGFR less than 30 mL/min/1.73 m2 (or if serum creatinine greater than 265 micromol/L). Avoid in Paget's disease, treatment of postmenopausal osteoporosis and osteoporosis in men if eGFR less than 35 mL/min/1.73 m2. Dose adjustments as described under dose.

Conception and contraception Contraindicated in women of child-bearing potential.

Pregnancy: Avoid—toxicity in animal studies.

Breastfeeding Avoid—no information available.

Adverse effects: Common or very common: Appetite decreased, chills, flushing**,** Anaphylactic shock, anxiety, arrhythmias, chest pain, circulatory collapse, cough, drowsiness, dry mouth, dyspnoea, haematuria, hyperhidrosis, hypertension, hypotension, leucopenia, muscle spasms**,** proteinuria, respiratory disorders, sensation abnormal, sleep disorder, stomatitis, syncope, thrombocytopenia tremor, vision blurred, weight increased**,** Confusion, Fanconi syndrome acquired**,** pancytopenia**,** Acute phase reaction

Renal impairment and renal failure have been reported, ensure patient is hydrated before each dose and assess renal function.

Interactions with other medicines: Calcium containing IV fluids, Magnesium or Phosphorus, Bumetamide, Furosemide, Mineral supplements, Increased risk of nephrotoxicity on concurrent use with other nephrotoxic agents including: Aceclofenac, acyclovir, amikacin, amphotericin, bacitracin, capreomycin, carboplatin, cephalexin, cefixime, ceftazidime, ciclosporin, cisplatin, dexketoprofen, diclofenac, etoricoxib, ganciclovir, gentamicin, ibuprofen, gentamicin, ketoprofen, mefenamic acid, indomethacin, meloxicam, methotrexate, oxaliplatin, piroxicam, streptomycin, tacrolimus, trimethoprim, vancomycin, tenofovir disoproxil, zidovudine.

Notes:

» Monitoring requirements: Correct disturbances of calcium metabolism (e.g., vitamin D deficiency, hypocalcaemia) before starting. Monitor serum electrolytes, calcium, phosphate and magnesium. Monitor renal function in patients at risk, such as those with pre-existing renal impairment, those of advanced age, those taking concomitant nephrotoxic drugs or diuretics, or those who are dehydrated.

» Directions for administration: When used for Prevention of skeletal related events in advanced malignancies involving bone or Tumour-induced hypercalcaemia For IV infusion, infuse over at least 15 minutes, administer as a single IV solution in a separate infusion line. If using 4 mg/5 mL concentrate for solution for infusion or preparing a reduced dose of 4 mg/100 mL solution for infusion for patients with renal impairment, dilute requisite dose according to product literature.

» When used for Paget's disease of bone or Osteoporosis (including corticosteroid-induced osteoporosis) in men and postmenopausal women For IV infusion, give via a vented infusion line over at least 15 minutes.

» Patient and Caregiver advice: A patient reminder card should be provided (risk of osteonecrosis of the jaw)

10. Antiparkinsonism Medicines

Benzhexol Hcl (Trihexyphenidyl)

ATC code: N04AA01

Tablet, 5 mg, LOU 2

Indications and dose

Adult

Parkinsonism, drug-induced extrapyramidal symptoms (but not tardive dyskinesia), oral: 1 mg daily, then increased in steps of 2 mg every 3–5 days, adjusted according to response; maintenance 5–15 mg daily in 3–4 divided doses; not recommended for use in Parkinson's disease because of toxicity in the elderly and the risk of aggravating dementia; maximum 20 mg per day.

Elderly: Lower end of range preferable, not recommended for use in Parkinson's disease because of toxicity in the elderly and the risk of aggravating dementia.

Precautions: May affect performance of skilled tasks (e.g., driving). Avoid abrupt withdrawal in patients on long-term treatment. Use with caution in hepatic and renal impairment, cardiovascular disease, elderly, hypertension, prostatic hypertrophy, psychotic disorders.

Pregnancy/breastfeeding: Use only if potential benefit outweighs risk in pregnancy and avoid in breastfeeding.

Adverse effects: Angle- closure, glaucoma, anxiety, blurred vision, confusion, constipation, dizziness, dry mouth, euphoria, hallucinations, impaired memory, nausea, rash, restlessness, tachycardia, urinary retention and vomiting

Interactions with other medicines: Drugs with anti-muscarinic effects

Notes: Tablets should be taken with or after food.

Biperiden

ATC code: N04AAO2

Injection, 5mg (lactate) in 1 mL ampule, LOU4

Tablet, 2mg (Hydrochloride), LOU4

Indications and dose

Adult

Doses are expressed in terms of the relevant salt.

Symptomatic treatment of parkinsonism, oral: 2mg three or four times daily increased according to response to a maximum of 16mg daily.

Drug-induced extrapyramidal symptoms (like other antimuscarinics has no value against tardive dyskinesias), oral: 2mg one to three times daily

By IM or slow IV injection:

2.5-5mg as a single dose, if necessary, the same dose can be repeated after 30 minutes. The maximum daily dose amounts to 10-20mg.

For elderly patients: Lower initial dose and increase gradually to the lowest effective dose.

Paediatric

There is limited information on the use. Use only under specialist advice.

Contraindications: Hypersensitivity to biperiden or its excipients.

Hepatic & Renal impairment: There have been no reports in literature.

Pregnancy& Breastfeeding: Insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore use unless benefits outweigh the risks.

Adverse effects: In higher doses; excitement, agitation, fear, confusion, mental delusions (delirious syndromes and hallucination), sleeplessness, Influence on sleep phases. Fatigue, dizziness and disturbance of memory, accelerated pulse (palpitations), dryness of mouth, nausea, muscle twitching.

Interactions with other medicines: Any other medicines for the treatment of movement disorders, any other Parkinson drugs, quinidine, metoclopramide

Levodopa + Carbidopa

ATC code: N04BA02

Tablet, 100 mg + 10 mg, 250 mg + 25 mg, LOU 4

Indications and dose

Adult

All forms of Parkinsonism except drug-induced Parkinsonism, oral: Initially 100–125 mg (expressed as L-Dopa) 3–4 times daily

Contraindications: Hypersensitivity, Narrow-angle glaucoma (tablets), Concurrent administration of nonselective MAOIs or use within last 14 days

Pregnancy/breastfeeding: Limited data. Weigh benefits against the risks.

Adverse effects: agranulocytosis, suicidal tendencies, involuntary movements, hypotension, arrhythmias, hypertension, GI bleeding.

Interactions with other medicines (*indicates serious): *Isocarboxazid, *phenelzine, *procarbazine, *selegiline, *selegiline transdermal

Pramipexole

ATC code: N04BC05

Tablet (scored), 180 micrograms base, 700 micrograms base, LOU 4

Indications and dose

Adult

Idiopathic Parkinson's disease, oral: 0.375 mg/day in 3 divided doses gradually increased not more frequently than 5–7 days

Contraindications: Hypersensitivity

Precautions: Psychotic disorders, risk of visual disorders (ophthalmological testing recommended), severe cardiovascular disease

Pregnancy/breastfeeding: Insufficient data on the effects of the drug on the foetus and/or mother during pregnancy and breastfeeding therefore its use is not recommended.

Adverse effects: Hallucinations, dyskinesia, dry mouth, somnolence, insomnia, constipation, dizziness, orthostatic hypotension.

11. Medicines For Alzheimer's Disease and Dementia

Donepezil

ATC code: N06DA02

Tablet, 5 mg, 10 mg, LOU 4

Indications and dose

Adult

Management of mild to moderate dementia due to Alzheimer's disease, oral: Initiated at 5 mg/day (once-a-day dosing); following a one-month clinical assessment of treatment at 5 mg/day, the dose can be increased to 10 mg/day (once-a-day dosing); the maximum recommended daily dose is 10 mg.

Contraindications: Hypersensitivity to donepezil or to piperidine derivatives

Precautions: risk of bleeding especially in patients with gastric ulcer and those on NSAIMs, may cause anorexia and/or weight loss, history of asthma or obstructive pulmonary disease, history of seizures, urinary tract obstruction, cardiac conduction abnormalities.

Hepatic and renal impairment: Has not been studied

Pregnancy/Breastfeeding: Insufficient data on the effects of the drug on the foetus and/or mother during pregnancy and breastfeeding therefore its use is not recommended.

Adverse effects: nausea, trouble sleeping, aggression, diarrhea, feeling tired, muscle cramps, abnormal heart rhythms, difficulty emptying urine from the bladder, and seizures.

Interactions with other medicines (*indicates serious)

*amiodarone, *arsenic trioxide, *artemether, *artemether/lumefantrine, *azithromycin, *bedaquiline, *chlorpromazine, *citalopram, *Clarithromycin, erythromycin, *hydroxychloroquine, *lithium, *lopinavir, *moxifloxacin, *nilotinib, *ondansetron, *oxaliplatin, *pazopanib, *procainamide, *quetiapine, *quinine, *solifenacin, *sotalol, alfuzosin, amitriptyline, bentropine, ciprofloxacin, clozapine, diltiazem, efavirenz, escitalopram, fluconazole, fluoxetine, goserelin, granisetron, imipramine, ketoconazole, itraconazole, leuprolide, levofloxacin, loperamide, olanzapinevecuronium, venlafaxine, voriconazole.

Notes:

- Taken at bedtime, with or without food
- Donepezil is not recommended for use in children and adolescents below 18 years of age.

Memantine

ATC code: N06DX01

Tablet, 5 mg, LOU 4

Indications and dose

Adult

Management of moderate dementia due to Alzheimer's disease when acetyl cholinesterase inhibitors are contraindicated or not tolerated. First choice in treatment of severe dementia; dose titration, oral:

Maximum daily dose is 20 mg per day; to reduce the risk of undesirable effects, the maintenance dose is achieved by upward titration of 5 mg per week over the first 3 weeks as follows:

- Week 1 (day 1–7): 5 mg per day for 7 days
- Week 2 (day 8–14): 10 mg per day for 7 days
- Week 3 (day 15–21): 15 mg per day for 7 days
- From week 4 on: 20 mg per day
- Maintenance dose: 20 mg per day

Contraindications: Hypersentivity to memantine, renal failure and hepatic disease.

Precautions: Use caution in cardiovascular disease, seizure disorder, ophthalmic disease, liver and/or kidney impairment

Pregnancy/Breastfeeding: Insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Adverse Effects: Headache, constipation, sleepiness, and dizziness, blood clots, psychosis, heart failure.

Interactions with other medicines (*Indicates serious):

*dextromethorphan, *ketamine, acetazolamide, aluminium hydroxide, amantadine, amiodarone, calcium carbonate, cimetidine, digoxin, dofetilide, procainamide, quinidine, ranitidine, sodium bicarbonate, sodium citrate/citric acid, sodium lactate, tenofovir DF, vandetanib. diltiazem, hydrochlorothiazide, metformin, methyclothiazide, midodrine, ofloxacin, pramipexole, quinine, sulfamethoxazole, triamterene, trimethoprim, verapamil

Rivastigmine

ATC code: NO6DAO3

Capsule 1.5mg, LOU4

Indications and dose

Symptomatic treatment of mild to moderate severe dementia in patients with idiopathic Parkinson's disease, oral

Adult

Initially 1.5mg twice daily, increased in steps of 1.5mg twice daily with meals, dose to be increased at intervals of at least 2 weeks according to response and tolerance; usual dose 3-6mg twice daily (max per dose 6mg twice daily), if treatment interrupted for more than several days, re-titrate from 1.5mg twice daily.

Paediatric

Not recommended

Contraindications: Hypersensitivity to the active ingredient, or to any of the excipients or other carbamate derivatives.

Precautions:

- Cholinesterase inhibitors should be prescribed with care to patients with a history of asthma

or obstructive pulmonary disease.

- Elderly: acetylcholinesterase inhibitors potentially inappropriate in patients with a known history of persistent bradycardia (heart rate > 60 beats per minute), heart block, recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate (risk of cardiac conduction failure, syncope and injury).
- Rivastigmine may cause increased gastric acid secretions. Care should be exercised in treating patients with active gastric or duodenal ulcers or patients predisposed to these conditions.
- Cholinomimetics may induce or exacerbate urinary obstruction and seizures. Caution is recommended in treating patients predisposed to such diseases.

Renal and hepatic impairment: No dose adjustment is necessary for patients with mild to moderate renal or hepatic impairment. However, due to increased exposure in these populations, closely titrate according to individual tolerability as patients with clinically significant renal or hepatic impairment might experience more dose dependent adverse reactions.

Pregnancy: No clinical data on exposed pregnancies are available. In pregnant animals, rivastigmine and/or metabolites crossed the placenta. It is not known if this occurs in humans. Rivastigmine should not be used during pregnancy unless clearly necessary.

Breastfeeding: In animals, rivastigmine is excreted into milk. It is not known if rivastigmine is excreted in to human milk. Therefore, women on rivastigmine should not breastfeed.

Adverse effects: Anxiety, loss of appetite, arrhythmias, asthenia, dehydration, diarrhea, dizziness, drowsiness, fall, gastrointestinal discomfort, headache, hyperhidrosis, hypersalivation, hypertension, movement disorders, nausea, skin reactions, syncope, tremor, urinary incontinence, urinary tract infection, vomiting, weight decrease, aggression, gait abnormal, hallucinations, sleep disorder.

Interactions with other medicines: Antidepressants, including amitriptyline, fluoxetine, Nortriptyline, paroxetine, antihistamines, ipratropium, Monoamine oxidase Inhibitors (MAOIs), potassium chloride, tiotropium.

12. Medicines Affecting The Blood

12.1. Antianemics

Darbepoetin Alfa

ATC code: BO3XAO2

Injection, 25mcg prefilled syringe, LOU4

Injection, 40mcg prefilled syringe, LOU4

Indications and dose

Adult

Symptomatic anemia associated with chronic renal failure in patients on dialysis, by SC injection: Initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose to be given once weekly or once every 2 weeks,

- reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2g/100ml over 4weeks or if haemoglobin concentration exceeds 12g/100ml,
- if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose,
- when changing route give same dose then adjust according to weekly or fortnightly hemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment.

Symptomatic anemia associated with chronic renal failure in patients not on dialysis, by SC injection: Initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose given once weekly,

- reduce dose by approximately 25% if rise in hemoglobin concentration exceeds 2g/100ml over 4 weeks or if hemoglobin concentration exceeds 12g/100ml,
- if hemoglobin concentration continues to rise, despite dose reduction, suspend treatment until hemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose,
- when changing route give same dose then adjust according to weekly or fortnightly hemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment.

Symptomatic anemia in adults with non-myeloid malignancies receiving chemotherapy, by SC injection: Initially 6.75 micrograms/kg every 3 weeks, alternatively initially 2.25 micrograms/kg once weekly,

- if response is inadequate after 9 weeks further treatment may not be effective,
- if adequate response is obtained then reduce dose by 25-50%,
- reduce dose by approximately 25-50% if rise in hemoglobin concentration exceeds 2g/100ml over 4 weeks or if hemoglobin concentration exceeds 12g/100ml,
- if hemoglobin concentration continues to rise despite dose reduction, suspend treatment until hemoglobin concentration decreases and restart at a dose approximately 25% lower than the previous dose.
- Discontinue approximately 4 weeks after ending chemotherapy.

Pediatric

Symptomatic anemia associated with chronic renal failure in patients on dialysis, by SC injection

Child 11-17 years: dosing as for adult population.

Symptomatic anemia associated with chronic renal failure in patients not on dialysis, by SC injection:

Child 11-17 years: Initially 450 nanograms/kg once weekly, alternatively initially 750 nanograms/kg every 2 weeks, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose can be given once weekly, every 2 weeks, or once a month,

- Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL,
- If haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose,
- When changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment

Contraindications: Hypersensitivity to the active substance or to any excipients listed and poorly controlled hypertension.

Precautions: Aluminium toxicity (can impair the response to erythropoietin), concurrent infection (can impair the response to erythropoietin), correct factors that contribute to the anemia of chronic renal failure, such as iron or folate deficiency, before treatment during (increase in unfractionated or low molecular weight heparin dose may be needed), during dialysis (increase in unfractionated or low molecular weight heparin dose may be needed), epilepsy, inadequately treated or poorly controlled blood pressure, ischemic vascular disease, malignant disease.

Hepatic impairment: Manufacturer advices caution (no information available).

Renal impairment: In patients with chronic renal failure, maintenance hemoglobin concentration should not exceed the upper limit of the target hemoglobin concentration.

Pregnancy: There are no adequate and well-controlled studies in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. No alteration of fertility was detected.

Caution should be exercised when prescribing to pregnant women.

Breastfeeding: It is unknown whether it is excreted in human milk. Caution should be exercised when prescribing to pregnant women.

Adverse effects: Hypersensitivity, oedema, arthralgia, embolism and thrombosis, headache, hypertension (dose-dependent), influenza like illness, stroke, seizure.

Interactions with other medicines:

Probenecid, lithium, loop diuretics, aminoglycosides, digitalis.

Notes:

» Treatment in neonates and infants has not been studied in randomized clinical trials. Clinical trails have been conducted in children over 1 years, refer to summary product characteristics for dosing in this population.

Erythropoietin (Alfa or Beta) Stimulating Agents

ATC code: B03XA01

Injection (prefilled syringe), 2000 IU, LOU 4

Indications and dose

Epoetin alfa

Adult

Anemia due to end stage kidney disease, chemotherapy, major surgery, or other chronic illnesses

Patients with CKD on dialysis, by IV or SC injection: 50 to 100 units/kg 3 times weekly initially; treatment initiated when haemoglobin level is <10g/dL; reduce or interrupt dose if haemoglobin level approaches or is > 11g/dL

Patients with CKD NOT on dialysis

» Treatment is initiated only when the haemoglobin level is <10g/dL.

» In addition to haemoglobin <10g/dL, the rate of haemoglobin decline indicates a likelihood of requiring red blood cell transfusion, or the goal is to reduce the risk of alloimmunization and/or other red blood cells transfusion-related risks.

» Dose is reduced or interrupted, and lowest dose of epoetin sufficient to reduce the need for red blood cell transfusions is used if haemoglobin is >10g/dL.

Paediatric

CKD associated anaemia, by IV or SC injection:

Child < 1 month: Safety and efficacy not established

Child >1 month: 50 units/kg 3 times weekly initially; If patient on dialysis, IV route is recommended

Treatment should be initiated when haemoglobin level is <10g/dL; reduce or interrupt dose if haemoglobin level approaches or exceeds >11g/dL

Zidovudine- associated anaemia, by IV or SC injection:

Child < 8 months: Safety and efficacy not established

Child 8 months – 17 years: 50 to 400units/kg 2 to 3 times weekly

Chemotherapy related anaemia, by IV injection:

Child < 5 years: Safety and efficacy not established

Child 5 years – 18 years: 600 units/kg (Maximum: 40000units) once

Dose is reduced by 25% if haemoglobin increases >1g/dL in any two week period OR reaches a level to avoid red blood cell transfusion.

Dose is withheld if haemoglobin exceeds level needed to avoid red blood cell transfusion and initiated at 75% the initial dose when haemoglobin approaches a level where red blood cell transfusions may be required

Dose is increased to 900 units/kg weekly (Maximum 60000 units) after initial 4 weeks of treatment if haemoglobin increases by <1g/dL and remains <10g/dL

Treatment is discontinued if no response after 8 weeks or if red blood cell transfusions are required

Epoetin Beta

Adult

Anaemia in Patients with Chronic Kidney Disease, by IV/SC

Treatment with erythropoietin beta is divided into two stages:

1. Correction phase

By subcutaneous administration

The recommended starting dose is 60 IU/kg body weight/week, administered as a single weekly injection or in up to 7 divided doses. The dose may be increased every 4 weeks by 60 IU/kg body weight/week if the haemoglobin increase is not adequate (Hb < 1.5 g/L per week).

By intravenous administration

The initial dose is 120 IU/kg body weight/week, administered in 3 divided doses. The dose may be raised after 4 weeks to 240 IU/kg body weight/week. If further increments are needed, they should be at 60 IU/kg body weight/week, at monthly intervals.

2. Maintenance phase

To maintain haemoglobin between 10–12 g/dL the dose is initially reduced to half of the previously administered amount.

In the case of subcutaneous administration, the weekly dose can be given as a single injection or in up to 7 divided doses. Patients who are stable on a once weekly dosing regimen may be switched to once every 2 weeks administration.

Dose adjustment

- Increases in dose should NOT be made more frequently than once a month. The dose for each patient should be adjusted so that the haemoglobin concentration does not exceed 12 g/dL. If the haemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25–50%.
- If the haemoglobin continues to increase, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be re-initiated at a dose approximately 25–50% below the previous dose. If the haemoglobin increases by more than 1g/dL in any 2-week period, the dose should be decreased by approximately 25–50%.
- The maximum dose should not exceed 720 IU/kg body weight/week.

Treatment of Anaemia in Patients with Non-Myeloid Malignancies, by SC: Treatment should not be commenced unless the haemoglobin falls below 10–11 g/dL. The recommended initial dose is 450 IU/kg body weight/week, administered as a single weekly injection or in 3 to 7 divided doses. If after 4 weeks, patient does not show a satisfactory response in terms of haemoglobin values, then the dose should be doubled. The therapy should be continued up to 4 weeks after the end of chemotherapy. The maximum dose should not exceed 900 IU/kg body weight/week.

Note: If haemoglobin falls by more than 1g/dL in the next cycle of chemotherapy despite concomitant erythropoietin beta therapy, further administration may not be effective.

Paediatric

Prevention of Anaemia of prematurity, SC

Infant: The solution is administered subcutaneously at a dose of 750 IU/kg body weight/week administered in 3 divided doses.

Treatment should be commenced as early as possible, preferably by day 3 of life.

Note: Premature infants who have already been transfused prior to erythropoietin beta treatment are not likely to benefit as much as non-transfused infants. The treatment should last for 6 weeks.

Treatment of Anaemia in Patients with Non-Myeloid Malignancies, SC

Child all ages: Refer to adult dosing

Anaemia in Patients with Chronic Kidney Disease, IV/SC

Child all ages: Refer to adult dosing.

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Patients who develop pure red cell aplasia following treatment with any erythropoietin.

Uncontrolled hypertension. All contraindications associated with autologous blood pre-donation programmes. Use in patients scheduled for major elective orthopaedic surgery and not participating in an autologous blood pre-donation programme is contraindicated in patients with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent MI or cerebral vascular accident. Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis.

Precautions: All other causes of anaemia (iron, folate, or vitamin B_{12} deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be evaluated and treated prior to initiating therapy with Erythropoetin (alpha or beta) stimulating agents, and when deciding to increase the dose. In order to ensure optimum response to Erythropoetin (alpha or beta) stimulating agents, adequate iron stores should be assured and iron supplementation should be administered if necessary.

Adverse Effects: Joint pain, rash, vomiting, and headache, heart attacks, stroke, increased cancer growth, or pure red cell aplasia.

Interactions with other medicines: Limited data

Ferrous Salt

ATC code: B03AA, B03AB

Oral liquid (drops), equivalent to 25 mg (iron as sulphate)/mL, LOU 2

Tablet, (f/c) 60 – 65 mg elemental iron, LOU 2

Indications and dose

Adult

Iron deficiency anaemia, oral: elemental iron, 100–200 mg daily in divided doses

Prevention of iron deficiency anaemia (in those at particular risk- women), oral: elemental iron 60 mg daily; folic acid may also be given

Paediatric

Iron deficiency anaemia, oral

Neonate: 2–4 mg/kg of elemental iron daily, given in 2–3 divided doses

Infant and **child:** 3–6 mg/kg (maximum 200 mg) of elemental iron daily, given in 2–3 divided doses

Prevention of iron deficiency anaemia (in those at particular risk), oral

Child under 5 years: 1–2 mg/kg (maximum 30 mg) of elemental iron daily

Child over 5 years: 30–60 mg of elemental iron daily; folic acid may also be given.

Contraindications: Haemosiderosis, haemochromatosis, any form of anaemia not caused by iron deficiency, patients receiving repeated blood transfusions, parenteral iron therapy.

Precautions: Should not be administered for longer than 6 months, peptic ulcer, regional enteritis, ulcerative colitis, intestinal strictures, diverticula, overdosage

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Constipation, diarrhoea, dark stools, nausea, epigastric pain, GI irritation. Long-term or excessive administration may cause haemosiderosis.

Interactions with other medicines (*indicates serious):

- Calcium salts: reduced absorption of oral ferrous salts.
- Ciprofloxacin: absorption of ciprofloxacin reduced by oral ferrous salts.
- *Dimercaprol: avoid concomitant use.
- Doxycycline: absorption of oral ferrous salts reduced by doxycycline, absorption of doxycycline reduced by oral ferrous salts.
- Levodopa: absorption of levodopa may be reduced by oral ferrous salts.
- Levofloxacin: absorption of levofloxacin reduced by oral ferrous salts.
- Levothyroxine: absorption of levothyroxine reduced by oral ferrous salts (give at least 2 hours apart).
- Methyldopa: oral ferrous salts reduce hypotensive effect of methyldopa.
- Ofloxacin: absorption of ofloxacin reduced by oral ferrous salts.
- Penicillamine: oral ferrous salts reduce absorption of penicillamine.
- Zinc sulphate: absorption of zinc and of oral ferrous salts reduced.

Notes:

- **Patient advice:** Although iron preparations are best absorbed on an empty stomach, they may be taken after food to reduce GI adverse effects, they may discolour stools. Liquid preparations containing iron salts should be well diluted with water (and if possible swallowed through a drinking straw to prevent discoloration of the teeth).
- Iron preparations are an important cause of accidental overdose in children and as little as 20 mg/kg of elemental iron can lead to symptoms of toxicity. Adequate precautions including the use of child-resistant containers should be taken to store iron preparations to prevent such overdoses.
- Iron content in artificial formula feeds should be taken into account when considering iron supplementation.
- 1 mg elemental iron = approximately 3 mg dried ferrous sulphate = approximately 9 mg ferrous gluconate.
- Compliance may be increased by giving the total daily dose as a single daily dose. However, GI adverse effects are increased and split daily doses may be better tolerated.
- Although iron preparations are best absorbed on an empty stomach, they may be taken after food to reduce GI adverse effects. They may discolour stools.
- Liquid preparations containing iron salts should be well diluted with water. If possible, swallow through a drinking straw and brush teeth after administration to prevent discoloration of the teeth.
- Temporary discoloration of the teeth can be minimized by brushing the teeth with baking soda.
- Increase fibre in diet to minimize constipation.

Ferrous Salt + Folic Acid

ATC code: B03AD

Tablet, 60–65 mg elemental iron + 400 micrograms folic acid, LOU 2

Indications and dose

Adult

Severe anaemia, oral: elemental iron 120 mg + folic acid 400 micrograms daily for 3 months

Prevention of iron and folate deficiencies in pregnancy, oral: Elemental iron 100 mg + folic acid 350–400 micrograms daily throughout pregnancy

Paediatric

Severe anaemia, oral

Child under 2 years: elemental iron 25 mg + folic acid 100–400 micrograms daily for 3 months

Child 2–12 years: elemental iron 60 mg + folic acid 400 micrograms daily for 3 months **Contraindication:** Iron metabolism disorder causing increased iron storage, an overload of iron in the blood, in hemolytic anemia, an ulcer from too much stomach acid, gastritis, ulcerative colitis, diverticular disease, excess iron due to repeated blood transfusions.

Precautions: Avoid taking antacids, tetracycline antibiotics, dairy products, tea, or coffee within 2 hours before or after this medication because they will decrease its effectiveness.

Adverse effects: Constipation, diarrhea, stomach cramps, or upset stomach may occur, darkened stools.

Interactions with other medicines: Antibiotics including penicillamine, chloramphenicol, quinolones such as ciprofloxacin, norfloxacin, bisphosphonates, e.g., alendronate, levodopa, methyldopa, thyroid replacement drugs, e.g., levothyroxine, hydantoins, e.g., phenytoin.

Notes:

- Take tablets or capsules with a full glass of water. Do not lie down for at least 10 mins after taking the medicine.

Folic Acid

ATC code: B03BB01

Tablet, 400 micrograms, LOU 1

Tablet, 5 mg, LOU 1

Indications and dose

Adult

Folate-deficiency, megaloblastic anaemia, oral: 5 mg daily for 4 months (in pregnancy continued to term), up to 15 mg daily may be necessary in malabsorption states

Prevention of first occurrence of neural tube defects, oral: 400 micrograms daily before conception and during the first 12 weeks of pregnancy

Prevention of recurrence of neural tube defects, oral: 5 mg daily (reduce to 4 mg daily, if suitable preparation available) from at least 4 weeks before conception until 12th week of pregnancy

Paediatric

Folate deficiency, megaloblastic anaemia, oral

Neonate to **child 1 year**: Initially 500 micrograms/kg (maximum 5 mg) once daily for up to 4 months; up to 10 mg once daily may be required in malabsorption states

Child over 1 year: 5 mg daily for 4 months; up to 15 mg daily may be required in malabsorption states

Haemolytic anaemia, oral

Child 1 month–12 years: 2.5–5 mg once daily

Contraindications: Should never be given without vitamin B12 in undiagnosed megaloblastic anaemia or other vitamin B12 deficiency states because of risk of precipitating subacute combined degeneration of the spinal cord, folate-dependent malignant disease.

Precautions: women receiving antiepileptic therapy (need counselling before starting folic acid).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Rare: GI disturbances, subacute combined degeneration of the spinal cord if given without vitamin B12 for vitamin B12 deficiency states.

Interactions with other medicines (*indicates serious):

* Phenobarbital: plasma concentration of phenobarbital possibly reduced.

* Phenytoin: plasma phenytoin concentration possibly reduced.

Sulfasalazine: possibly reduced absorption of folic acid.

Sulfadoxine + pyrimethamine: possibly reduced efficacy of sulfadoxine + pyrimethamine.

Hydroxocobalamin (Vitamin B_{12})

ATC code: B03BA03

Injection, 1 mg/1 mL amp, LOU 4

Indications and dose:

Used in the treatment of megaloblastic anaemia due to vitamin B12 deficiency (pernicious anaemia).

Adult

Megaloblastic anaemia without neurological involvement, by IM: Initially 1 mg 3 times a week for 2 weeks, then 1 mg every 2–3 months

Megaloblastic anaemia with neurological involvement, by IM: Initially 1 mg on alternate days until no further improvement occurs, then 1 mg every 2 months.

Prophylaxis of macrocytic anaemias, by IM: 1 mg every 2–3 months.

Tobacco amblyopia and Leber optic atrophy, by IM injection: 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months.

Paediatric

Megaloblastic anaemia without neurological involvement, by IM injection

Child 1 month–12 years: initially 250 micrograms–1 mg three times weekly for 2 weeks, then 250 micrograms once weekly until the blood count is normal, then 1 mg every 3 months if required.

Child over 12 years: initially 1 mg 3 times a week for 2 weeks, then 1 mg every 3 months.

Megaloblastic anaemia with neurological involvement, by IM injection

Child 1 month–12 years: initially 1 mg on alternate days until no further improvement occurs, then 1 mg every 2 months.

Prophylaxis of macrocytic anaemias, by IM injection

Child: 1 mg every 2–3 months.

Tobacco amblyopia and Leber optic atrophy, by IM injection

Child: 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months. **Contraindications**: Hypersensitivity to hydroxocobalamin or any of its components.

Precautions: Should not be given before diagnosis confirmed except in emergencies, monitor serum potassium levels (arrhythmias secondary to hypokalaemia in early therapy).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common: Nausea, headache, dizziness, pain at injection site. **F**ever, chills, hot flushes, hypokalaemia during initial treatment. Rare: Hypersensitivity reactions including rash and pruritus, anaphylaxis, acneiform and bullous eruptions.

Interactions with other medicines (*indicates serious):

Chloramphenicol: response to Hydroxycobalamine reduced.

Iron Sucrose

ATC code: B03AB02

Injection, Iron (as iron sucrose) 20 mg per 1 mL (100 mg/5 mL solution for injection vials), LOU 4

Indications and dose

Adult

Complex of ferric hydroxide with sucrose containing 2% (20 mg/mL) of iron

Iron-deficiency anaemia, by slow IV injection or IV infusion: Doses calculated according to body weight and iron deficit.

» For intermittent IV infusion, dilute to a concentration of 1 mg/mL with sodium chloride 0.9%, give at a rate not exceeding 6.67 mg/min

(consult product literature).

» For slow IV injection, give undiluted at a rate of 1 mL/min, do not exceed 10 mL (200 mg iron) per injection.

Contraindications: Low blood pressure, chronic excess iron in the blood, iron overload.

Precautions: Allergy to the drug or its inactive ingredients.

Hepatic impairment: Manufacturer advises caution—monitor iron status to avoid iron overload, avoid where iron overload is a precipitating factor (particularly porphyria cutanea tarda).

Renal Impairment: Recommended doses appear safe for adults with CKD

Adverse effects: Asthenia, drowsiness, urine discolouration, cold sweat, confusion, level of consciousness decreased, thrombophlebitis. Muscle cramps, nausea, vomiting, strange taste in the mouth, diarrhea, constipation, headache, cough, back pain, joint pain, dizziness, or swelling of the arms/legs may occur. Pain, swelling, or redness at the injection site may occur.

12.2. Medicines Affecting Coagulation

12.2.1. Coagulant Medicines

Phytomenadione (Vitamin K1)

ATC code: B02BA01

Injection, 1 mg/1 mL in 0.2-mL amp, LOU 2

Injection, 10 mg/mL in 1-mL amp, LOU 4

Indications and dose

Adult

Antagonist to warfarin, IM or slow IV: 10 mg

Paediatric

Prophylaxis of haemorrhagic disease of the newborn, IM

Neonate: 0.5–1 mg as single dose at birth

Prophylaxis of haemorrhagic disease of the newborn, oral

Neonate: 2 mg followed by a second dose after 4–7 days and, for breastfed babies, a third dose after 1 month

Prophylaxis of haemorrhagic disease of the newborn, IV

Pre-term neonate: 400 micrograms/kg (maximum 1 mg)

Note: The IV route is preferred by some in pre-term neonates of very low birth weight, but it does not provide the prolonged protection of the IM injection; any babies receiving IV vitamin K should be given subsequent oral doses (as per oral dosing, above).

Haemorrhagic disease of the newborn, IV

Neonate: 1 mg with further doses if necessary every 8 hours

Warfarin-induced hypoprothrombinaemia with no or minor bleeding, IV

Child 1 month–12 years:15–30 micrograms/kg (maximum 1 mg) as a single dose, repeated as necessary

Warfarin-induced hypoprothrombinaemia: Reversal of anticoagulation or if significant bleeding, treatment of haemorrhage associated with vitamin K deficiency, IV

Child 1 month–12 years: 250–300 micrograms/kg (maximum 10 mg) as a single dose

Contraindications: None

Precautions: Hepatic impairment, not an antidote to heparin.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Higher doses may be required for adequate response.

Adverse effects: Hypersensitivity reactions including flushing, dyspnoea, bronchospasm, dizziness, hypotension and respiratory or circulatory collapse which may be due to polyethoxylated castor oil surfactant in some injection formulations, rather than due to phytomenadione.

Interactions with other medicines (*indicates serious):

* Warfarin: vitamin K antagonizes anticoagulant effect of warfarin.

Notes

IV injections should be given very slowly (risk of vascular collapse). In infants with cholestatic disease, vitamin K must be given either intramuscularly or intravenously because oral absorption is likely to be impaired.

IV preparations can usually be given orally. Please check specific product information.

Tablets may be chewed.

Tranexamic Acid

ATC code: B02AA02

Tablet, 500 mg, LOU 4

Injection, 100 mg/1 mL in 5-mL amp, LOU 2

Indications and dose

Adult

Local fibrinolysis, oral: 1–1.5 g 2–3 times a day; alternatively, 15–25 mg/kg 2–3 times a day

Local fibrinolysis, initially by slow IV injection: 0.5–1 g 2–3 times a day, to be administered at a rate not exceeding 100 mg/min, followed by (by continuous IV infusion) 25–50 mg/kg if required, dose to be given over 24 hours

Menorrhagia, oral: 1 g 3 times a day for up to 4 days, to be initiated when menstruation has started, maximum 4 g per day

Hereditary angioedema, oral: 1–1.5 g 2–3 times a day for short-term prophylaxis of hereditary angioedema;

tranexamic acid is started several days before planned procedures, which may trigger an acute attack of hereditary angioedema (e.g., dental work) and continued for 2–5 days afterwards

Epistaxis, oral: 1 g 3 times a day for 7 days

General fibrinolysis, by slow IV injection: 1 g every 6–8 hours, alternatively 15 mg/kg every 6–8 hours, dose to be given at a rate not exceeding 100 mg/min

Prevention and treatment of significant haemorrhage following trauma, initially by slow IV injection: Loading dose 1 g to be given over 10 minutes; treatment should commence within 8 hours of injury, followed by (by IV infusion) 1 g to be given over 8 hours

Contraindication: Fibrinolytic conditions following disseminated intravascular coagulation (unless predominant activation of fibrinolytic system with severe bleeding), history of convulsions, thromboembolic disease

Precautions: Irregular menstrual bleeding (establish cause before initiating therapy). massive haematuria (avoid if risk of ureteric obstruction). Patients receiving oral contraceptives (increased risk of thrombosis). Menorrhagia Before initiating treatment for menorrhagia, exclude structural or histological causes or fibroids causing distortion of uterine cavity.

Renal impairment: Dose adjustments Reduce dose—consult product literature for details.

Hepatic impairment: Regular liver function tests in long-term treatment of hereditary angioedema.

Adverse effects: Common or very common: Diarrhoea (reduce dose), nausea, vomiting. Uncommon: Allergic dermatitis. Rare or very rare: Colour vision change (discontinue), embolism and thrombosis. Frequency not known: Seizure (more common at high doses), visual impairment (discontinue). Specific adverse effects with IV use: Hypotension, malaise (on rapid IV injection)

Interactions with other medicines:
Anticoagulants such as warfarin, heparin, drugs that prevent bleeding including factor XI, estrogens, tibolone, tretinoin, NSAIMs such as aspirin (high dose), ibuprofen, naproxen that may increase your risk of bleeding.

Notes:

» Low-dose aspirin should be continued if prescribed by your doctor for specific medical reasons such as heart attack or stroke prevention.

12.2.2. Anticoagulant Medicines

Enoxaparin

ATC code: B01AB05

Injection (prefilled and calibrated syringe), 40 mg/0.4 mL, 80 mg/0.8 mL, LOU 4

Indications and dose

Prophylaxis of deep vein thrombosis and ischemic complications which may lead to pulmonary embolism

Adult

Abdominal surgery and medical patients during acute illness, SC injection: 40 mg once a day with the initial dose given 2 hours prior to surgery

Hip or knee replacement surgery, SC injection:: 30 mg every 12 hours

Deep vein thrombosis with or without pulmonary embolism, SC injection: 1 mg/kg every 12 hours

Paediatric: Specialist use only

Contraindications: Hypersensitivity to enoxaparin sodium, heparin or its derivatives, including other low molecular weight heparins or to any of the excipients

History of immune mediated heparin-induced thrombocytopenia) within the past 100 days or in the presence of circulating antibodies. Active clinically significant bleeding and conditions with a high risk of haemorrhage, including recent haemorrhagic stroke, GI ulcer, presence of malignant neoplasm at high risk of bleeding, recent brain, spinal or ophthalmic surgery, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Spinal or epidural anaesthesia or loco-regional anaesthesia when enoxaparin sodium is used for treatment in the previous 24 hours.

Precautions: Limited data

Adverse Effects: Atrial fibrillation, heart failure, lung edema, pneumonia, injection site ecchymoses and hematomas.

Interactions with other medicines:

Nonsteroidal anti-inflammatory drugs (NSAIMs), such as aspirin, ibuprofen, or naproxen. Platelet inhibitors, such as clopidogrel, prasugrel, ticagrelor, or dipyridamole. Herbal supplements, such as ginkgo biloba, fish oil, garlic, ginseng, and ginger. These drugs can decrease your platelets increasing the risk of bleeding.

Heparin Sodium

ATC code: B01AB01

Injection, 5000 units/mL, 5-mL vial, LOU 4

Indications

Treatment and prophylaxis of deep-vein thrombosis and pulmonary embolism, unstable angina, ischaemic stroke; short-acting injectable anticoagulant

Dose

Treatment of deep-vein thrombosis and pulmonary embolism: loading dose of 5000 IU (10,000 IU in severe pulmonary embolism) followed *by continuous IV infusion* of 15–25 IU/kg/hour or by *SC injection* of 15,000 IU every 12 hours, laboratory monitoring is essential, preferably on a daily basis and dose adjusted accordingly

Low-body-weight adult: lower loading dose, then *by continuous IV infusion*, 15–25 IU/kg/hour or *by SC injection*, 250 IU/kg every 12 hours.

Prophylaxis in general surgery, by SC

5000 IU for 1 dose, given 2 hours before surgery, then every 8–12 hours for 7 days or until patient is ambulant (monitoring not needed)

Thromboprophylaxis during pregnancy, by SC: 5000–10,000 IU every 12 hours

Paediatric

Treatment of deep-vein thrombosis and pulmonary embolism, by IV injection

Neonate to **Child 1 year**: initially 75 units/kg (50 units/kg if < 35 weeks corrected age), then *by continuous IV infusion*, 25 units/kg/hour, adjusted according to APTT or anti-Factor Xa

Child 1–12 years: initially 75 units/kg, then *by continuous IV infusion* 20 units/kg/hour, adjusted according to APTT or anti-Factor Xa

By SC injection

Child 1 month–12 years: 250 units/kg every 12 hours adjusted according to APTT or anti-Factor Xa.

Prophylaxis in general surgery, by SC injection:

Child 1 month–12 years: 100 units/kg (maximum 5000 units) twice daily, adjusted according to APTT or anti-Factor Xa.

Contraindications: Hypersensitivity to heparin, haemophilia and other haemorrhagic disorders, thrombocytopenia, peptic ulcer, recent cerebral haemorrhage, severe hypertension, severe liver or renal disease, after major trauma or recent surgery (especially to eye or nervous system), acute bacterial endocarditis.

Precautions: Hepatic impairment and renal failure, hypersensitivity to low molecular weight heparins, spinal or epidural anaesthesia (risk of spinal haematoma), diabetes mellitus, acidosis, concomitant potassium-sparing drugs (increased risk of hyperkalaemia).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Hepatic impairment with impaired haemostasis: increased risk of haemorrhage. Reduce dose in severe impairment.

Adverse effects: Common: Hyperkalaemia, injection site reactions, haematoma if given IM. Haemorrhage, haematuria, thrombocytopenia. Rare: Immune-mediated thrombocytopenia usually developing 6–10 days after commencement of therapy (requires immediate withdrawal of heparin), skin necrosis, hypersensitivity reactions including urticaria, angioedema and anaphylaxis, osteoporosis after prolonged use, alopecia, rebound hyperlipidaemia after withdrawal, priapism.

Interactions with other medicines (*indicates serious):

*Acetylsalicylic acid: enhanced anticoagulant effect of heparin.

Enalapril: increased risk of hyperkalaemia.

*Glyceryl trinitrate: anticoagulant effects reduced by infusion of glyceryl trinitrate.

Ibuprofen: possibly increased risk of bleeding.

Notes

- For continuous IV infusion, dilute with glucose 5% or sodium chloride 0.9%.
- Laboratory monitoring of coagulation activity, preferably on a daily basis, involves determination of the APTT or of the anti-Factor Xa concentration. Local guidelines on recommended APTT for neonates and children should be followed.
- If haemorrhage occurs, it is usually sufficient to withdraw heparin, but if rapid reversal of heparin effects is required, protamine sulphate is a specific antidote.
- Not intended to cover prosthetic heart valve management in pregnancy, which requires specialist management).

Rivaroxaban

ATC code: B01AF01

Tablet, 10 mg, 15 mg, 20 mg, LOU 5

Indications and dose

Adult

Use for patients with atrial fibrillation and pulmonary embolism. The duration of therapy and dose selection should be individualized after careful assessment of the treatment benefit against the risk for bleeding.

Treatment and prevention of recurrent deep vein thrombosis and pulmonary embolism, oral: Day 1–21, 15 mg twice daily, then day 22 onward 20 mg once daily

Prevention of recurrent DVT and PE, following completion of at least 6 months of therapy for DVT or PE, oral: 10 mg once daily or 20 mg once daily

Atrial fibrillation, oral: 20 mg once daily with evening meal

Paediatric: Safety and efficacy not established.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Active clinically significant bleeding. Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent GI ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Concomitant treatment with any other anticoagulants, e.g., unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives, oral anticoagulants, except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. Pregnancy and breastfeeding.

Precautions: The product may contain inactive ingredients that may cause allergic reactions. History of hepatic or renal disease, blood disorders, bleeding disorders including anaemia, haemophilia and thrombocytopenia.

Hepatic impairment: Avoid in hepatic disease with coagulopathy and clinically relevant bleeding risk, including patients with moderate to severe cirrhosis.

Renal impairment: Caution if creatinine clearance 15–29

mL/minute; avoid if creatinine clearance less than 15 mL/minute. Use with caution if concomitant use of drugs that increase plasma rivaroxaban concentration (consult product literature). Dose adjustments:

- *When used for treatment of DVT or PE, following the first 21 days of treatment:* Consider reducing dose to 15 mg once daily if creatinine clearance 15–49 mL/minute and the risk of bleeding outweighs the risk of recurrent deep-vein thrombosis or pulmonary embolism.
- *When used for prophylaxis of recurrent DVT or PE:* Consider reducing to 15 mg once daily if creatinine clearance 15–49 mL/minute and the risk of bleeding outweighs the risk of recurrent deep-vein thrombosis or pulmonary embolism.
- *For prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation:* Reduce dose to 15 mg once daily if creatinine clearance 15–49 mL/minute

Pregnancy: Manufacturer advises avoid—toxicity in animal studies.

Breastfeeding: Manufacturer advises avoid—present in milk in animal studies.

Adverse Effects: Bleeding, spinal hematoma, anaphylaxis.

Interactions with other medicines

Aspirin, mifepristone, antiplatelet drugs such as clopidogrel, "blood thinners" such as warfarin, enoxaparin, antidepressants including SSRIs such as fluoxetine, selective serotonin- and norepinephrine-reuptake inhibitors, such as desvenlafaxine/venlafaxine. Cobicistat, conivaptan, certain azole antifungals (itraconazole, ketoconazole, posaconazole), rifamycins (such as rifampin), HIV protease inhibitors (such as lopinavir, ritonavir), St. John's wort, drugs used to treat seizures (such as carbamazepine, phenytoin, phenobarbital) affect the elimination of the drug from the body.

Notes

- RESTRICTED: Not for use in pregnancy and patients with prosthetic mitral valves
- Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.

Warfarin

ATC code: B01AA03

Tablet (scored), 1 mg, 3mg, 5 mg (sodium salt), LOU 4

Indications and dose

Adult

Wherever possible, the baseline PT should be determined before the initial dose is given, but the initial dose should not be delayed while awaiting the result. Induction dose may need to be altered according to condition (e.g., hepatic impairment, cardiac failure), concomitant interacting drugs, and if baseline INR is above 1.3; prophylaxis and treatment of thromboembolic disorders.

Prophylaxis of embolization in rheumatic heart disease and atrial fibrillation, prophylaxis after insertion of prosthetic heart valve, prophylaxis and treatment of venous thrombosis and pulmonary embolism, transient ischaemic attacks, oral: Start with 5 mg or 10 mg and titrate based on INR on day 3. Initial dose dependent on patient age and bleeding risk. Goal is INR of 2–3 for thrombosis and 2.5–3.5 for patients with mechanical valves.

Note: In acute thrombosis, it is important to bridge warfarin with heparin (low molecular-weight heparin/UFH)

Paediatric

Neonate (under specialist advice): 200 micrograms/kg as a single dose on day 1, then 100 micrograms/kg once daily for the next 3 days.

- However, if INR is still below 1.4, continue to use 200 micrograms/kg once daily.
- If INR is above 3, change to 50 micrograms/kg once daily; if INR is above 3.5, omit dose. Adjust ongoing therapy in accordance with INR.
- Usual maintenance 100–300 micrograms/kg once daily (may need up to 400 micrograms/kg once daily, especially if bottle fed, see Notes).

Child 1 month–12 years: 200 micrograms/kg (maximum 10 mg) as a single dose on day 1, then 100 micrograms/kg (maximum 5 mg) once daily for the next 3 days.

- However, if INR is still below 1.4, continue to use 200 micrograms/kg (maximum 10 mg) once daily.
- If the INR is above 3, change to 50 micrograms/kg (maximum 2.5 mg) once daily; if INR is above 3.5, omit dose. Adjust ongoing therapy in accordance with INR.
- Usual maintenance 100–300 micrograms/kg once daily (may need up to 400 micrograms/kg once daily especially if bottle fed, see Notes).

Contraindications: Pregnancy, peptic ulcer, severe hypertension, bacterial endocarditis.

Precautions: Hepatic impairment or renal failure, recent surgery, avoid cranberry juice (risk of potentiating anticoagulant effect).

Renal impairment: Use with caution, avoid in severe impairment.

Hepatic impairment: Avoid in severe impairment, especially if PT already prolonged.

Adverse effects: Common: Haemorrhage. Rare: Hypersensitivity, rash, alopecia, diarrhoea, unexplained drop in haematocrit, systemic cholesterol microembolism ('purple toes syndrome'), skin necrosis, jaundice, hepatic dysfunction, nausea, vomiting, pancreatitis.

Interactions with other medicines (*indicates serious): *Acetylsalicylic acid: increased risk of bleeding due to antiplatelet effect.

*Alcohol: enhanced anticoagulant effect with large amounts of alcohol, major changes in alcohol consumption may affect anticoagulant control.

Allopurinol: anticoagulant effect possibly enhanced.

*Amitriptyline: enhanced or reduced anticoagulant effect.

Amoxicillin: studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of amoxicillin.

Ampicillin: studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of ampicillin.

*Azathioprine: anticoagulant effect possibly reduced.

*Azithromycin: possibly enhanced anticoagulant effect of warfarin.

*Carbamazepine: accelerated metabolism of warfarin (reduced anticoagulant effect).

Cefazolin: possibly enhanced anticoagulant effect.

*Cefixime: possibly enhanced anticoagulant effect.

*Ceftazidime: possibly enhanced anticoagulant effect.

*Ceftriaxone: possibly enhanced anticoagulant effect.

*Chloramphenicol: enhanced anticoagulant effect.

*Ciprofloxacin: enhanced anticoagulant effect.

*Clomipramine: enhanced or reduced anticoagulant effect.

*Contraceptives, oral: antagonism of anticoagulant effect by estrogens and progestogens.

*Dexamethasone: anticoagulant effect possibly enhanced or reduced (high-dose dexamethasone enhances anticoagulant effect).

*Doxycycline: anticoagulant effect possibly enhanced.

*Erythromycin: enhanced anticoagulant effect.

*Etoposide: possibly enhanced anticoagulant effect.

*Fluconazole: enhanced anticoagulant effect.

*Fluorouracil: anticoagulant effect possibly enhanced.

*Fluoxetine: anticoagulant effect possibly enhanced.

*Glibenclamide: possibly enhanced hypoglycaemic effects and changes to anticoagulant effect.

*Griseofulvin: reduced anticoagulant effect.

*Hydrocortisone: anticoagulant effect possibly enhanced or reduced (high-dose hydrocortisone enhances anticoagulant effect).

*Ibuprofen: anticoagulant effect possibly enhanced.

*Levamisole: anticoagulant effect possibly enhanced.

*Levofloxacin: possibly enhanced anticoagulant effect.

*Levonorgestrel: antagonism of anticoagulant effect.

Levothyroxine: enhanced anticoagulant effect.

*Medroxyprogesterone: antagonism of anticoagulant effect.

*Mercaptopurine: anticoagulant effect possibly reduced.

Metronidazole: enhanced anticoagulant effect.

*Miconazole: enhanced anticoagulant effect.

*Nevirapine: enhanced or reduced anticoagulant effect.

*Norethisterone: antagonism of anticoagulant effect.

*Ofloxacin: enhanced anticoagulant effect.

Paracetamol: prolonged regular use of paracetamol possibly enhances anticoagulant effect.

*Phenobarbital: metabolism of warfarin accelerated (reduced anticoagulant effect).

*Phenytoin: accelerated metabolism of warfarin (possibility of reduced anticoagulant effect, but enhancement also reported).

*Phytomenadione: antagonism of anticoagulant effect by phytomenadione.

*Prednisolone: anticoagulant effect enhanced or reduced (high-dose prednisolone enhances anticoagulant effect).

Proguanil: isolated reports of enhanced anticoagulant effect.

*Quinidine: anticoagulant effect may be enhanced.

*Rifampicin: accelerated metabolism of warfarin (reduced anticoagulant effect).

*Ritonavir: plasma concentration possibly increased by ritonavir.

Saquinavir: possibly enhanced anticoagulant effect.

*Silver sulfadiazine: enhanced anticoagulant effect.

*Simvastatin: enhanced anticoagulant effect.

*Sulfadiazine: enhanced anticoagulant effect.

*Sulfadoxine + pyrimethamine: enhanced anticoagulant effect.

*Sulfamethoxazole + trimethoprim: enhanced anticoagulant effect.

*Tamoxifen: enhanced anticoagulant effect.

*Testosterone: enhanced anticoagulant effect.

Trimethoprim: possibly enhanced anticoagulant effect.

Infuenza vaccine: effect of warfarin occasionally enhanced.

Valproic acid: anticoagulant effect possibly enhanced.

Cranberry juice and products: enhanced anticoagulant effect (cranberry flavonoids inhibit CYP2C9).

High doses of vitamin A, E or C: altered PT.

Notes:

- Serious and potentially fatal bleeding may occur, especially during initiation of treatment and with higher doses.
- This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.
- Monitoring It is essential that the INR be determined daily or on alternate days in the early days of treatment, and then at longer intervals (depending on response), then up to every 12 weeks.

- Infant formula is supplemented with vitamin K, which makes formula fed infants resistant to warfarin, they may need higher doses. Breast milk contains low concentrations of vitamin K and breastfed infants are more sensitive to warfarin.
- Avoid switching warfarin brands once desired therapeutic response has been achieved.
- **Target INR range:** generally, 2–3 for most indications, 2.5–3.5 for prosthetic heart valves and antiphospholipid antibody syndrome associated with thrombosis.
- Other considerations Warfarin antagonizes the effects of vitamin K and takes at least 48–72 hours for the anticoagulant effect to develop fully, if an immediate effect is required, heparin must be given concomitantly.
- Foods containing high amounts of vitamin K (such as beef liver, pork liver, green tea and green leafy vegetables) can reverse the anticoagulant effects of warfarin and affect therapeutic outcomes. A balanced diet is essential. Avoid large amounts of alfalfa, asparagus, broccoli, brussel sprouts, cabbage, cauliflower, green teas, kale, lettuce, spinach, turnip greens, watercress.
- High doses of vitamin A, E or C may alter PT, use fish oils or omega 3 with caution and avoid large amounts of liver, avocado, soy protein, soybean, papain.
- Avoid herbal teas or remedies (e.g., tonka beans, melilot, woodruff) as these contain natural coumarins and may increase the effect of warfarin.**Other Medicines For Haemoglobinopathies**

Deferasirox

ATC code: V03AC03

Tablet, 100 mg, 400 mg, LOU 4

Indications and dose

Adult

Transfusion-related chronic iron overload in patients with beta thalassaemia major who receive frequent blood transfusions (7 mL/kg/month or more of packed red blood cells) (specialist use only), oral: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood—consult product literature, then adjust in steps of 3.5–7 mg/kg every 3–6 months; maintenance dose adjusted according to serum-ferritin concentration; maximum 28 mg/kg per day, usual maximum 21 mg/kg

Transfusion-related chronic iron overload when desferrioxamine is contraindicated or inadequate in patients with beta thalassaemia major who receive infrequent blood transfusions (less than 7 mL/kg/month of packed red blood cells) (specialist use only), oral: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood—consult product literature, then adjust in steps of 3.5–7 mg/kg every 3–6 months; maintenance dose adjusted according to serum-ferritin concentration; maximum 28 mg/kg per day, usual maximum 21 mg/kg

Transfusion-related chronic iron overload when desferrioxamine is contraindicated or inadequate in patients with other anaemias (specialist use only), oral: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood—consult product literature, then adjust in steps of 3.5–7 mg/kg every 3–6 months; maintenance dose adjusted according to serum-ferritin concentration; maximum 28 mg/kg per day, usual maximum 21 mg/kg

Chronic iron overload when desferrioxamine is contraindicated or inadequate in non-transfusion-dependent thalassaemia syndromes (specialist use only), oral: Initially 7 mg/kg once daily, then adjust in steps of 3.5–7 mg/kg every 3–6 months; maintenance dose adjusted according to serum-ferritin concentration and liver-iron concentration (consult product literature); maximum 14 mg/kg per day

Chronic iron overload due to transfusions, oral:

- Treatment should only be initiated with evidence of chronic iron overload (i.e., transfusion of ≥100 mL/kg of packed red blood cells [e.g., ≥20 units for a 40-kg individual] and serum ferritin consistently >1,000 micrograms/L).
- Exjade™: Initial 20 mg/kg once daily
- Maintenance: Adjust dose every 3 to 6 months based on serum ferritin trends, adjust by 5 or 10 mg/kg/day, titrate to individual response and treatment goals. In patients not adequately controlled with 30 mg/kg/day, doses up to 40 mg/kg/day may be considered for serum ferritin levels persistently >2,500 micrograms/L and not decreasing over time (doses >40 mg/kg/day are not recommended).
- Consider interrupting therapy for serum ferritin consistently <500 micrograms/L.

Chronic iron overload in nontransfusion-dependent thalassemia syndromes, oral

- Treatment should only be initiated with evidence of chronic iron overload (hepatic iron concentration ≥5 mg Fe/g dry weight and serum ferritin >300 micrograms/L).
- Exjade™: Initial 10 mg/kg once daily; consider increasing to 20 mg/kg once daily after 4 weeks if baseline hepatic iron concentration is >15 mg Fe/g dry weight.
- Maintenance, dependent upon serum ferritin measurements (monthly) and hepatic iron concentrations (every 6 months): If serum ferritin is 5 mg Fe/g dry weight: An interruption of treatment should be considered or if serum ferritin is 3 to 7 mg Fe/g dry weight: Continue treatment at a dose ≤10 mg/kg/day. If serum ferritin >7 mg Fe/g dry weight: Increase dose to 20 mg/kg/day, maximum dose: 20 mg/kg/day,

Paediatric

Transfusion-related chronic iron overload when desferrioxamine is contraindicated or inadequate in patients with beta thalassaemia major who receive frequent blood transfusions (7 mL/kg/month or more of packed red blood cells), oral

Child 2–5 years: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood, then adjusted in steps of 3.5–7 mg/kg every 3–6 months; maintenance dose adjusted according to serum-ferritin concentration, maximum 28 mg/kg per day, usual maximum 21 mg/kg

Transfusion-related chronic iron overload in patients with beta thalassaemia major who receive frequent blood transfusions (7 mL/kg/month or more of packed red blood cells), oral

Child 6–17 years: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood, then adjusted in steps of 3.5–7 mg/kg every 3–6 months; maintenance dose adjusted according to serum-ferritin concentration, maximum 28 mg/kg per day, usual maximum 21 mg/kg

Transfusion-related chronic iron overload when desferrioxamine is contraindicated or inadequate in patients with beta thalassaemia major who receive infrequent blood transfusions (less than 7 mL/kg/month of packed red blood cells), oral

Child 2–17 years: Initially 7–21 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood—consult product literature, then adjusted in steps of 3.5–7 mg/kg every 3–6 months, maintenance dose adjusted according to serum-ferritin concentration; maximum 28 mg/kg per day; Usual maximum 21 mg/kg

Contraindications: Hypersensitivity to the active substance or to any of the excipients, combination with other iron chelator therapies as the safety of such combinations has not been established, patients with estimated CrCl of <60 mL/min.

Precautions: Elderly (increased risk of adverse effects), history of liver cirrhosis, not recommended in conditions which may reduce life expectancy (e.g., high-risk myelodysplastic syndromes), platelet count less than 50 × 109/L, risk of GI ulceration and haemorrhage, unexplained cytopenia—consider treatment interruption

Hepatic impairment: Manufacturer advises caution in moderate impairment, avoid in severe impairment. Dose adjustments Manufacturer advises reduce initial dose considerably then gradually increase to max. 50% of normal dose in moderate impairment.

Renal impairment: Manufacturer advises avoid if estimated CrCl less than 60 mL/min. Dose adjustments Manufacturer advises reduce dose if CrCl less than 90 mL/min and serum creatinine increased by more than 33% of baseline measurement on 2 consecutive occasions—consult product literature.

Adverse Effects: Common or very common: Constipation, diarrhoea, GI discomfort, headache, nausea, skin reactions, urine abnormalities, vomiting. Uncommon: Anxiety, cataract, cholelithiasis, dizziness, fatigue, fever, GI disorders, GI haemorrhage (including fatal cases), hearing impairment, hepatic disorders, laryngeal pain, maculopathy, oedema, renal tubular disorders, sleep disorder. Rare or very rare: Optic neuritis, SCARs. Frequency not known: Acute kidney injury, alopecia, anaemia aggravated, hyperammonaemic encephalopathy, hypersensitivity vasculitis, lens opacity, leucopenia, metabolic acidosis, nephritis tubulointerstitial, nephrolithiasis, neutropenia, pancreatitis acute, pancytopenia, renal tubular necrosis, thrombocytopenia

Interactions with other medicines:

Aluminium Hydroxide: May diminish the therapeutic effect of Deferasirox. Anticoagulants: May enhance the adverse/toxic effect of Deferasirox. Specifically, the risk for GI ulceration/irritation or GI bleeding may be increased. Corticosteroids: May enhance the adverse/toxic effect of Deferasirox.

Notes

- Deferasirox is an oral iron chelator.
- The following should be monitored: baseline serum creatinine twice and CrCl once before initiation of treatment, weekly in the first month after treatment initiation or modification, then monthly thereafter, proteinuria before treatment initiation then monthly thereafter, and other markers of renal tubular function as needed, liver function before treatment initiation, every 2 weeks during the first month of treatment, then monthly thereafter, eye and ear examinations before treatment and annually during treatment, serum-ferritin concentration monthly. For film-coated (f/c) tablets, manufacturer advises tablets may be crushed and sprinkled on to soft food (yoghurt or apple sauce), then administered immediately.

Deferoxamine Mesilate

ATC code: V03AC01

Powder for injection, 500 mg in vial, LOU 4

Indications and dose

Adult

For IV infusion, give continuously or intermittently in glucose 5% or sodium chloride 0.9%. Reconstitute with water for injection to a concentration of 100 mg/mL, dilute with infusion fluid.

Iron poisoning, by continuous IV infusion: Initially up to 15 mg/kg/hour, max. 80 mg/kg in 24 hours, dose to be reduced after 4–6 hours; in severe cases, higher doses may be given on advice from the National Poisons Information Service

Aluminium overload in dialysis patients, by IV infusion: Consult product literature or local protocols.

Chronic iron overload (low iron overload), by SC infusion: Dose should reflect degree of iron overload

Chronic iron overload (established overload) by SC infusion: 20–50 mg/kg daily

Paediatric

Chronic iron overload (low iron overload), SC or IV infusion

Infant or **child:** Initially up to 30 mg/kg over 8–12 hours, on 3–7 days per week; *for established iron overload*, dose is usually between 20 and 50 mg/kg daily; dose should reflect the degree of iron overload; use the lowest effective dose

Diagnosis of iron overload, IM

Child: 500 mg

Contraindications, precautions, adverse effects and interactions with other medicines: See Deferoxamine section 5 – Antidotes and other substances used in poisonings

Notes

» Eye and ear examinations before treatment and at 3-month intervals during treatment.

Hydroxycarbamide (Hydroxyurea)

ATC code: L01XX05

Capsule,250 mg, 500 mg, LOU 4

Oral solution (Extemporaneously prepared): 100 mg/45 mL, LOU 4

Indications and dose

Adult

Cytoreduction, e.g., myeloproliferative neoplasms with leukocytosis, polycythaemia vera or essential thrombocytosis,

Polycythaemia vera (specialist use only), oral: Initially 15–20 mg/kg daily, adjusted according to response; for information on dose adjustment based on haematocrit and platelet count, consult product literature; usual dose 500–1000 mg daily, dosage should be based on actual or ideal body weight, whichever is less

Essential thrombocythaemia (specialist use only), oral: Initially 15 mg/kg daily, adjusted according to response; for information on dose adjustment based on platelet count and white cell count, consult product literature; dosage should be based on actual or ideal body weight, whichever is less

Chronic myeloid leukaemia (specialist use only), oral: Initially 40 mg/kg daily, then reduced to 20 mg/kg daily, adjusted according to response; for information on dose adjustment based on white cell count, consult product literature; dosage should be based on actual or ideal body weight, whichever is less

Cancer of the cervix (specialist use only), oral: 20–30 mg/kg daily, alternatively 80 mg/kg every 3 days; for information on dose adjustment based on platelet count, white cell count, and actual or ideal body weight, consult product literature

Sickle-cell disease [prevention of recurrent vaso-occlusive crises] (initiated by a specialist), oral: Initially 15 mg/kg daily, increased in steps of 2.5–5 mg/kg daily, dose to be increased every 12 weeks according to response; usual dose 15–30 mg/kg daily; maximum 35 mg/kg per day.

Note: consult manufacturer product literature for dosing increment recommendations.

Paediatric

Sickle cell disease, oral

Child: 20 mg/kg orally once a day, increase 5 mg/kg/day every 8 weeks or if a painful crisis occurs; maximum dose is 35 mg/kg/day

Contraindications: Hydroxycarbamide is contraindicated in patients with marked bone marrow depression, i.e., leukopenia (< 2500 WBC/mm3) or thrombocytopenia (< 100,000/mm3), or severe anaemia.

Precautions: Leg ulcers (review treatment if cutaneous vasculitic ulcerations develop).

Hepatic impairment: Manufacturer advises caution in mild to moderate impairment, avoid in severe impairment (unless used for malignant conditions).

Renal impairment: In sickle-cell disease:

» Avoid if eGFR less than 30 mL/min/1.73 m2. Use with caution in malignant disease.

» Reduce initial dose by 50% if eGFR less than 60 mL/min/1.73 m2.

Adverse Effects: Common or very common: Alopecia, anaemia, appetite decreased, asthenia, bone marrow disorders, chills, constipation, cutaneous vasculitis, dermatomyositis, diarrhoea, disorientation, dizziness, drowsiness, dyspnoea, dysuria, fever, GI discomfort, haemorrhage, hallucination, headache, hepatic disorders, leucopenia, malaise, mucositis, nail discolouration, nail disorder, nausea, neoplasms, neutropenia, oral disorders, pancreatitis, peripheral neuropathy, pulmonary oedema, red blood cell abnormalities, respiratory disorders, seizure, skin reactions, skin ulcers, sperm abnormalities, thrombocytopenia, vomiting. Rare or very rare: Cutaneous lupus erythematosus, gangrene, SLE. Frequency not known: Amenorrhoea, GI disorders, hypomagnesaemia, Parvovirus B19 infection, vitamin D deficiency, weight increased.

Interactions with other medicines

Concurrent use of hydroxycarbamide and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow depression or other adverse events reactions.

Live vaccines are predicted to increase the risk of generalized infection (possibly life-threatening) when given with hydroxycarbamide. Hydroxycarbamide increases the risk of toxicity when given with stavudine.

Notes

» Monitor renal and hepatic function before and during treatment.

» Monitor full blood count before treatment, and repeatedly throughout use, in sickle-cell disease monitor every 2 weeks for the first 2 months and then every 2 to 3 months thereafter (or every 2 weeks if on maximum dose).

» Patients receiving long-term therapy for malignant disease should be monitored for secondary malignancies. Patients receiving long-term therapy with hydroxycarbamide should be advised to protect skin from sun exposure.

13. Blood Products of Human Origin & Plasma Substitutes

13.1. Blood & Blood Components

Cryoprecipitate

ATC code: B02BD02

LOU5

Indications and dose

Adult

Cryoprecipitate is made from fresh blood plasma - a source of concentrated clotting factors including Factor VIII, von Willebrand factor and fibrinogen.

Dosing depends on patient clotting factor and requires routine monitoring to determine appropriate dose.

Fibrinogen Replacement

- 1 unit per 5kg patient weight will increase fibrinogen by about 100mg/dl.
- Number of bags = 0.2 x weight (kg) to provide about 100mg/dl fibrinogen
- In conditions with increased fibrinogen turnover, fibrinogen levels should be monitored to adjust dosing.

Factor XIII Replacement

- 1 unit per 5kg patient weight will provide 10Units/kg of factor XIII
- Number of bags = 0.2 x weight (kg)
- Factor XIII has a long half-life and can usually be dosed every 3-6 weeks. Dosing schedule can vary by patient.

Factor VIII Replacement (Consultation with a hematologist or hemostasis expert is recommended. Dosing depends on patient factor VIII (8) level and requires routine monitoring to determine appropriate dose).

- Patients with inhibitors may not have adequate response requiring increased dosing or other measures.
- In emergency situations, assume a desired increase of 100% for a loading dose. Dosing also depends on Plasma Volume (PV) which is a fraction of Total Blood Volume (TBV). TBV is typically estimated at 70 mL/kg, although it may vary based on age, sex, and body type.
  - TBV (mL) = 70 mL/kg x weight (kg)
  - PV (mL) = TBV x (1-Hct)
  - Number of bags = [Desired activity (%) – Current activity (%)] x PV / 80
- Dosing should be repeated every 8-12 hours but will vary with each patient. Factor VIII activity (%) target depends on the indication
- Post surgery or major trauma replacement may be required for up to 10 days to maintain hemostasis

Von Willebrand Factor Replacement

- Consultation with a hematologist or hemostasis expert is recommended. Dosing of 1 unit per 10kg patient weight will usually be enough to control bleeding
- Number of bags = 0.1 x weight (kg)
- Repeat dosing may be required every 8-12 hours for up to 3 days followed by once daily dosing. Follow clinically to adjust dosing and with appropriate lab studies available at your institution

Contraindications: should not be given for vitamin K deficiency or warfarin reversal if correction can safely be achieved using vitamin K supplementation. Should not be given for replacement of isolated factor or specific protein deficiencies if the appropriate factor concentrates are available. Relative contraindications are heart failure and pulmonary edema.

Adverse Effects: Hemolytic transfusion reactions. Febrile Non-Hemolytic reactions. Allergic reactions ranging from urticaria to anaphylaxis. Septic reactions. Transfusion related acute lung injury, circulatory overload. Transfusion associated graft versus host disease. Post-transfusion purpura.

Interactions with other medicines: Limited data.

Plasma Fresh-Frozen

ATC code: B05AX03

LOU 4

FFP is the acellular portion of blood that is frozen within 6–8 hours of donation; must be ABO-compatible with recipient's red blood cells

Indications and dose

- *Correction of congenital or acquired deficiencies of clotting factors (for which there is not a specific concentrate), when the PT or APTT ratio is >1.5*
- *Reconstitution of whole blood for exchange transfusions*
- *Treatment of bleeding due to multiple coagulation factor deficiencies, massive transfusion with coagulation abnormalities and bleeding due to warfarin therapy.*

Recommended therapeutic dose: 10–15 mL/kg of body weight over 2–4 hours; however, dose depends on the clinical situation and laboratory parameters

Contraindications: FFP should not be given for vitamin K deficiency or warfarin reversal if correction can safely be achieved using vitamin K supplementation.

FFP should not be given for replacement of isolated factor or specific protein deficiencies if the appropriate factor concentrates are available

Relative contraindications are heart failure and pulmonary edema.

Adverse Effects:

Hemolytic transfusion reactions

Febrile Non-Hemolytic reactions

Allergic Reactions ranging from urticaria to anaphylaxis

Septic Reactions

Transfusion Related Acute Lung Injury
Circulatory Overload

Transfusion Associated Graft Versus Host Disease

Post-transfusion Purpura.

Interactions with other medicines: Limited data.

Platelets

LOU 4

Indications and dose

Adult

Platelet transfusions may be given for thrombocytopenia or platelet dysfunction to treat active platelet-related bleeding or as prophylaxis in those at serious risk of bleeding.

Paediatric

Neonates and child <10 kg: Transfusion of 5–10 mL/kg should raise the platelet count by 40–50,000/mm3

Child >10 kg: Transfusion of 1 unit of whole blood-derived platelets per 10 kg should raise the platelet count by 50,000/mm3. Transfused platelets have a short life span and will need to be reinfused if platelet count is not achieved

Note: There may be a difference between apheresed platelets and those from conventionally single or pooled donor blood.

Contraindications

- Platelet transfusions in patients with autoimmune destruction of platelets such as immune thrombocytopenia should not be transfused in the absence of bleeding because the transfused platelets will be quickly removed similarly to the patient's own platelets without clinical benefit.
- Platelet transfusions are controversial in patients with Post Transfusion Purpura, since platelet specific antibodies against high frequency platelet antigens are part of the pathophysiology of this potentially fatal disorder.
- Platelet transfusions are contraindicated in patients with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, or heparin-induced thrombocytopenia. Although these conditions can have marked thrombocytopenia, they are generally pro-thrombotic and transfusion of platelets may "fuel the fire" if transfused as prophylaxis in the absence of significant bleeding.

Adverse Effects: See PFF above.

Red Blood Cells

LOU 4

Indications and dose

- Hb <13 g/dL if baby is less than 24 hours old or NICU/ventilation with high oxygen need
- Hb <11.0 g/dL and chronic oxygen dependence for neonates
- Chronic anemia
- Acute and preoperative blood loss
- Usually blood loss >20% estimated total blood volume

1 unit increases haemoglobin by 1 g/dL in average-sized adults without active bleeding or hemolysis, usually given over 1–2 hours but not longer than 4 hours; rarely necessary to transfuse to haemoglobin >10 g/dL; actively bleeding patients dosing and rate of administration varies depending on rate of bleeding and must be evaluated on a case-by-case basis

Contraindications

Should not be used to treat anemia that can be corrected with a non-transfusion therapy (e.g., iron therapy) unless immediate correction is urgently needed.

Adverse Effects

See PFF above

Notes

Use in pregnancy:

Pregnancy less than 36 weeks gestation.

- Hb<5.0 g/dL even without clinical signs of cardiac failure.
- Hb between 5.0 – 7.0 g/dL with clinical signs of cardiac failure.

Pregnancy greater than 36 weeks gestation.

- Hb<6.0 g/dL even without clinical signs of cardiac failure.
- Hb between 6.0– 8.0 g/dL with clinical signs of cardiac failure and or infection.

Elective Caesarian section.

- Hb 8.0 – 10.0 g/dL, confirm mother's blood group and confirm availability of blood in the laboratory or the blood transfusion unit.
- Hb <8.0 g/dL cross – match and reserve 2 units of blood.

Whole Blood

LOU 4

Indications and dose

As whole blood transfusion is limited to acutely hemorrhaging individuals, dosing should be based on the patient's clinical condition, estimated blood loss, and other measures being used to maintain hemodynamic stability.

Contraindications

Whole blood transfusions are not indicated when component specific therapy is available (i.e., use RBCs to treat anemia or use FFP to treat coagulopathy). The

use of whole blood when mono - component therapy is indicated and available could lead to complications such as volume overload.

Adverse Effects

See PFF above

13.2. Plasma-Derived Medicines

13.2.1. Human Immunoglobulins

Anti-D Immunoglobulin

ATC code: J06BB01

Powder for injection (+diluent), 750 IU/mL in 2-mL vial, LOU 4

Indications and dose

- *Sensitization of Rh o(D)-negative females to Rh o(D)-positive blood (prophylaxis) or Rh hemolytic disease of the newborn (prophylaxis)*
- *Rh o(D) immune globulin in Rh o(D)-negative females of child-bearing age or younger who have not been previously sensitized to the Rh o(D) erythrocyte factor and who may be exposed to the factor during one or more of the following events: the birth of an Rh o(D)-positive infant, incomplete pregnancy terminating in the delivery of an Rh o(D)-positive fetus (e.g., spontaneous or induced abortion or ruptured tubal pregnancy), amniocentesis, abdominal trauma during pregnancy, or trans placental hemorrhage, while carrying an Rh o(D)-positive fetus, or transfusion involving mismatched Rh o(D)-positive blood.*

Immune thrombocytopenia, IV: 50 micrograms/kg as a single injection

Antepartum prophylaxis, IM: 300 micrograms at ~28 weeks' gestation

Interactions: Live virus vaccines (antibodies contained in Rh o(D) immune globulin may interfere with the body's immune response to certain live virus vaccines, live virus vaccines, such as measles, mumps, and rubella (MMR), should be administered at least 3 months after administration of Rh o(D) immune globulin.

Adverse Effects: Anemia, renal insufficiency, intravascular hemolysis, fever.

Anti-Hepatitis B Immunoglobulin (HBIG)

ATC code: J06BB04

Injection, 100 IU/mL, LOU 4

Indications and dose

Use for sexual assault survivors and children born to hepatitis B+ mothers

Prevention of hepatitis B in case of accidental exposure in non-immunised subjects or in subjects who have had no more than a single dose of vaccine: At least 500 IU, depending on the intensity of exposure, as soon as possible after exposure, and preferably within 24–72 hours, although it should still be considered up to a week after exposure. If it is uncertain whether the source of the exposure is HBsAg-positive, the prophylactic use of human hepatitis B immunoglobulin is regarded as unnecessary.

Prevention of hepatitis B in the newborn, of a hepatitis B carrier-mother, at birth or as soon as possible after birth, preferably within 24 hours of birth: 30–100 IU/kg. The hepatitis B immunoglobulin administration may need to be repeated until seroconversion following vaccination.

Adverse Effects: Chest pain, dyspnoea, tremor, dizziness, facial oedema, glossitis, buccal ulceration, and arthralgia.

Anti-Rabies Immunoglobulin

ATC code: J06BB05

Injection, 200 IU/mL (5-mL vial), LOU 2

Indications and dose

Post-exposure prophylaxis of rabies infection in persons after exposure to scratches, bites or other injuries including mucous membrane contamination with infectious tissue, such as saliva, caused by a suspected rabid animal, by local infiltration or by IM injection; 20 units/kg (0.133 mL/kg)

NB: Human rabies immunoglobulin must always be used in combination with a rabies vaccine.

Administration notes:

- Post-exposure prophylaxis consists of a regimen of one dose of immunoglobulin and full courses of rabies vaccination. If vaccine is given but treatment with human rabies immunoglobulin is delayed, human rabies immunoglobulin should still be given up to seven days after starting the course of vaccine.
- The wound should be cleaned with soap and disinfectant.
- Injections of the immunoglobulin should preferably be administered in the bitten site.
- The immunoglobulin should be carefully infiltrated in the depth of and around the wound. Any remainder should be injected intramuscularly at a site distant from that used for the rabies vaccine. Multiple needle injections into the wound should be avoided.
- If the correct dose of rabies immunoglobulin is too small to infiltrate all wounds, as might be true of a severely bitten individual, it can be diluted in physiological buffered saline to ensure greater wound coverage.

Adverse Effects

Allergic reactions, fever, numbness, muscle weakness, headache, tachycardia, hypotension. Precautions/ special remarks: Avoid the gluteal muscle because of risk of injury to sciatic nerve.

Anti-Tetanus Immunoglobulin

ATC code: J06BB02

Injection, 500 IU in vial, LOU 4

Indications and dose

Adult

Prophylaxis, IM: 250 units single dose

Active tetanus, IM: 3000–6000 units

Paediatric

IM, prophylaxis

Child <7 years old: 4 units/kg or 250 units

Child over 7 years old: 250 units single dose

Treatment

Child: 3000–6000 units

Pregnancy: Use with caution if benefits outweigh risks

Adverse Effects: Allergic reactions, redness, warmth, edema, induration myalgia, arthralgia.

Interactions with other medicines

Immunosuppressive therapies may reduce response to vaccines.

Normal Immunoglobulin

ATC code: J06BA02

IV administration, 5%, 10% protein solution in 100-mL vial, LOU 5

Indications and dose

Replacement therapy in primary immunodeficiency, Kawasaki disease

Consult individual manufacturer's product literature for dose and administration recommendations for specific diseases; recommended doses may vary from those listed below.

Formulations from different manufacturers vary and should not be regarded as equivalent.

Paediatric

Replacement therapy in primary immune deficiencies, IV infusion

Child all ages: Initial loading dose, administer until serum IgG level is > 6 g/L

Replacement therapy in primary immune deficiencies, IV, IM, or *SC* (depending on formulation):

Child all ages: Maintenance dose, normally 400–800 mg/kg/month, titrated according to intercurrent infections or trough serum IgG level. IV doses may be given at 1-, 2-, 3-, or 4-week intervals. SC doses may be given at 1-, 2-, 3-, 4-, or 7-day intervals.

Kawasaki disease, IV infusion

Infant or **child:** 2 g/kg as a single dose, given over 10–12 hours; if signs and symptoms persist, retreatment with a second 2 g/kg infusion should be considered; must be used in combination with acetylsalicylic acid

Contraindications: Hypersensitivity to immunoglobulin or blood products.

Precautions: IM preparation Use with caution in patients with thrombocytopenia or coagulation disorders.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common: Nausea, vomiting, headache (may develop 24 hours after infusion), dizziness, dry mouth, chills, sweating, hypothermia, fever, eczema, rash, urticaria, hypotension, wheezing, anaphylactoid reactions, pain at the site of injection.

Rare: Immune haemolysis, aseptic meningism, increased plasma viscosity, hypercoagulopathy, renal impairment.

Interactions with other medicines (*indicates serious):

Live virus vaccines (MMR).

Notes

- IV human normal immunoglobulin may very rarely induce thromboembolic events and should be used with caution in those with risk factors for arterial or venous thrombotic events and in obese individuals.
- Normal immunoglobulin may interfere with the immune response to live virus vaccines which should therefore only be given at least 3 weeks before or 3 months after an injection of normal immunoglobulin (this does not apply to yellow fever vaccine since normal immunoglobulin does not contain antibody to this virus).
- IV compatibility: general advice is not to administer with any other drugs or IV fluids.
- IV infusion over 2–12 hours.
- Administration infusion rates of < 8 g per hour are recommended. Immunoglobulin should be administered under the supervision of an immunologist or other experienced physician. In general, this should be in a hospital with adequate facilities for monitoring the infusion as well as the condition for which it is being administered, until the patient is stable, when treatment at home can be considered after formal training in an expert centre.

13.2.2. Blood Coagulation Factors

Coagulation Factor VIII

ATC code: B02BD02

Powder for injection (extended half-life), 250 IU, 500 IU, 1000 IU, 2000 IU, LOU 4

Indications and dose

Control of haemorrhage in haemophilia A, acquired factor VIII deficiency, Von Willebrand's disease (if the product is not a recombinant)

Haemophilia A, slow IV infusion: Administer according to patient's needs and specific preparation used. For every 1 IU per kg body weight of factor VIII activity administered, factor VIII level should increase by 2 IU/mL (or 2%); calculated dosage should be adjusted to the actual vial size.

Calculation for units required, based on desired increase in factor VIII (% of normal):

IU required = body weight (kg) × 0.5 × desired increase in factor VIII (IU/mL or % of normal)

Note: This calculation assumes the patient's baseline factor VIII level is < 1%.

Contraindications: Previous anaphylactic reaction to factor VIII concentrate.

Precautions: Intravascular haemolysis after large or frequently repeated doses in patients with blood groups A, B or AB (less likely with high potency, highly purified concentrates).

Renal impairment: Dose adjustment not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common: Allergic reactions including chills and fever, headache, urticaria. Rare: Pseudothrombocytopenia, elevated ALT.

Interactions with other medicines (*indicates serious):

Activated prothrombin complex concentrates.

Notes:

- IV compatibility: general advice is not to administer with any other drugs or IV fluids.
- All plasma fractions should comply with the WHO requirements for the collection, processing and quality control of blood, blood components and plasma derivatives

Coagulation Factor IX

ATC code: B02BD01

Powder for injection (extended half-life), 250 IU, 500 IU, 1000 IU, LOU 4

Indications and dose

Replacement therapy for factor IX deficiency in haemophilia B or bleeding due to deficiencies of factors II, VII or X as well as IX, by slow IV infusion: Administer according to patient's needs and specific preparation used.

Calculation for units required, based on desired increase in factor IX (% of normal):

IU required = body weight (kg) × 1.0 × desired increase in factor IX (IU/mL or % of normal)

Paediatric

Neonate, infant or **child:**

Number of factor IX IU required = body weight (kg) × desired factor IX level increase (% normal) × 1.4 IU/kg. Consult product information as dosing may vary by brand.

Neonate, infant or **child:**

Number of factor IX IU required = body weight (kg) × desired factor IX level increase (% normal) × 1 IU/kg.

General guidelines

- Minor spontaneous haemorrhage, prophylaxis
- Desired levels of factor IX for haemostasis: 15–25%
- Initial loading dose to achieve desired level: Up to 20–30 IU/kg
- Frequency of dosing: Every 12–24 hours
- Duration of treatment: 1–2 days

Moderate haemorrhage

- Desired levels of factor IX for haemostasis: 25–50%
- Initial loading dose to achieve desired level: 25–50 IU/kg
- Frequency of dosing: Every 12–24 hours
- Duration of treatment: 2–7 days

Major haemorrhage

- Desired levels of factor IX for haemostasis: >50%
- Initial loading dose to achieve desired level: 30–50 IU/kg

Frequency of dosing: Every 12–24 hours, depending on half-life and measured factor IX levels (after 3–5 days, maintain at least 20% activity)

Duration of treatment: 7–10 days, depending upon nature of insult

Surgery

- Desired levels of factor IX for haemostasis: 50–100%
- Initial loading dose to achieve desired level: 50–100 IU/kg
- Frequency of dosing: Every 12–24 hours, depending on half-life and measured factor IX levels
- Duration of treatment: 7–10 days, depending upon nature of insult

Contraindications: Disseminated intravascular coagulation, hypersensitivity to mouse or hamster protein (if not the human form), fibrinolysis.

Precautions: Risk of thrombosis (probably less risk with highly purified preparations), because of this risk, use with caution in liver dysfunction, postoperative period, neonates or disseminated intravascular coagulation.

Renal impairment: Dose adjustment not necessary.

Hepatic impairment: Dose adjustment not necessary.

Adverse effects: Common: Allergic reactions including chills and fever, flushing, headache, nausea, vomiting, urticaria. Uncommon: Disseminated intravascular coagulation, thrombosis following high doses in haemophilia B patients.

Notes

- Both human and animal derived products are available.
- This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.
- IV compatibility: general advice is not to administer with any other drugs or IV fluids.
- All plasma fractions should comply with the WHO requirements for the collection, processing and quality control of blood, blood components and plasma derivatives.

13.3. Plasma Substitutes

Dextran-70

ATC code: B05AA05

Solution 6% for infusion, LOU4

Indications and dose

Adult

Shock, IV infusion: No more than 20mL/kg during first 24hours; then 10mL/kg/day

Paediatric

Shock, IV infusion: Initial dose 10mL/kg infused rapidly, no more than 20mL/kg/24hours, then no more than 10mL/kg/day, for not more than 5days

Contraindications: Hypersensitivity to dextran or corn products. Pulmonary edema, severe bleeding disorders, severe CHF, severe oliguria/anuria due to renal disease, cardiac decompensation, marked thrombocytopenia or hypofibrinogenemia

Precautions: Decreased urinary output secondary to shock, bowel surgery, dehydration, active hemorrhage, hypernatremia, pathological abdominal conditions, thrombocytopenia, monitor urinary output.

Hepatic and renal impairment: Extreme caution.

Pregnancy: Use with caution during pregnancy only if the benefit outweighs the risk to the fetus.

Breastfeeding: Not known if distributed into breast milk, avoid.

Adverse effects: Congenital heart failure, mild hypotension, tightness of chest, thrombocytopenia, anaphylaxis, phlebitis, acute renal failure, acidosis, pulmonary edema, wheezing.

Gelatin-Based Colloid

ATC code: B05AA06

Solution for infusion, 4%, LOU 4

Indications and dose

Plasma expander; use as alternative in patients with renal insufficiency and intolerance to starch plasma expanders

Gelatin-based colloid is administered intravenously; the volume and rate of infusion will depend on the patient's condition. When given rapidly, gelatin-based colloid should be warmed to no more than 37 °C, if possible. In severe acute blood loss, gelatin-based colloid may be given rapidly (500 mL in 5–10 minutes) until signs of hypovolaemia are relieved. When large volumes are given, suitable monitoring should be used to ensure that an adequate haematocrit is maintained (the haematocrit should not be allowed to fall below 25%) and that dilutional effects upon coagulation are avoided. (Expert haematological advice should be sought, especially in cases of massive blood loss.) For massive fluid loss, gelatin-based colloid may be used concomitantly with blood, the rate and amount of which depends on the clinical condition of the patient. The haemodynamic status of the patient should be monitored.

Adverse effects: Severe anaphylactic or anaphylactoid reaction, tremor, tachycardia, dyspnea, sweating, chills, pyrexia

Human Albumin Infusion

ATC code: B05AA01

Solution 5%, 20%, LOU 4

Indications and dose

Required for protein supplementation for patients with burn and other chronic wounds.

The dose required depends on the size of the patient, the severity of trauma or illness, and on continuing fluid and protein losses. Measures of adequacy of circulating volume and not plasma albumin levels should be used to determine the dose required. If human albumin is to be administered, haemodynamic performance should be monitored regularly, this may include arterial blood pressure and pulse rate, central venous pressure, pulmonary artery wedge pressure, urine output, electrolyte, haematocrit/haemoglobin.

Method of administration: Human albumin can be directly administered by the IV route, or it can also be diluted in an isotonic solution (e.g., 5% glucose or 0.9% sodium chloride). The infusion rate should be adjusted according to the individual circumstances and the indication. In plasma exchange, the infusion rate should be adjusted to the rate of removal.

Adverse Effects: Flush, urticaria, fever, nausea, shock.

Hydroxyethyl Starch

ATC code: B05AA07

Solution for infusion 6%, LOU 4

Indications and dose

Plasma expander

Daily dose and rate of infusion depend on the patient's blood loss, maintenance or restoration of hemodynamics, and hemodilution. Administer up to 50 mL/kg/day (equivalent to 3 g hydroxyethyl starch and 7.7 mEq Na per kg of body weight). This dose is equivalent to 3500 mL for a 70-kg patient. Give initial 10–20 mL by slow IV infusion and monitor for anaphylactoid reaction

Precautions: Do not use hydroxyethyl starch in critically ill adults (including sepsis). Use of hydroxyethyl starch increases risk of mortality and renal replacement therapy in critically ill adults.

Adverse Effects

Pruritus, elevation of serum amylase, anaphylactoid reactions: hypersensitivity, mild influenza-like symptoms, slow heart rate, fast heart rate, spasms of the airways, and non-cardiogenic pulmonary edema. It is also linked to a decrease in hematocrit and coagulation factors.

Polygeline

ATC code: B05AA06

Solution for infusion, 3.5% in 500-mL pack, LOU 4

Indications and dose

Prevention or treatment of shock associated with reduction in effective circulating blood volume due to hemorrhage, loss of plasma

Adjust dosage according to the patient's haemodynamic status. In the event of haemorrhage, replace the lost volume by the same volume of plasma substitute.

Precautions: When plasma substitutes are not available, use Ringer lactate (giving 3 times the lost blood volume).

Adverse effects: Allergic reactions, anaphylactic shock

14. Cardiovascular Medicines

14.1. Antianginal Medicines

Bisoprolol

ATC code: C07AB07

Tablet, 2.5 mg, 5 mg, LOU 4

Indications and dose

Adult

Hypertension, angina pectoris, supraventricular arrhythmias and acute/chronic coronary syndromes: 5 to 10 mg orally as a single daily dose; maximum recommended dose is 20 mg daily; dose reduction may be necessary in patients with hepatic or renal impairment

Heart failure: Initial oral dose of bisoprolol (as fumarate) is 1.25 mg once daily for 1 week, dose to be taken in the morning, then increased if tolerated to 2.5 mg once daily for 1 week, then increased if tolerated to 3.75 mg once daily for 1 week, then increased if tolerated to 5 mg once daily for 4 weeks, then increased if tolerated to 7.5 mg once daily for 4 weeks, then increased if tolerated to 10 mg once daily, maximum 10 mg per day

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Bisoprolol is contraindicated in chronic heart failure patients with: acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy, cardiogenic shock, second or third degree AV block (without a pacemaker), sick sinus syndrome, sinoatrial block, Symptomatic bradycardia, Symptomatic hypotension, severe bronchial asthma or severe chronic obstructive pulmonary disease, late stages of peripheral arterial occlusive disease and Raynaud's syndrome, untreated phaeochromocytoma, metabolic acidosis, hypersensitivity to the active substance or to any of the excipients.

Precautions: Ensure heart failure not worsening before increasing dose. Cessation of therapy with must not be done abruptly unless clearly indicated, because this may lead to transition worsening of heart condition

Hepatic Impairment: Dose adjustments:

- For angina or hypertension, initial dose of 2.5 mg. Consider maximum dose of 10 mg once daily in severe impairment. Use with caution.
- For heart failure, titrate dose with caution.

Renal Impairment: Dose adjustments Reduce dose if eGFR less than 20 mL/min/1.73 m2 (max. 10 mg daily).

Pregnancy: Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. Not recommended during pregnancy unless clearly necessary. If it must be used, then specialist advice required and the uteroplacental blood flow and foetal growth should be monitored. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects:

GI complaints such as nausea, vomiting, diarrhoea, constipation, dizziness, headache, bradycardia (in patients with chronic heart failure), worsening of pre-existing heart failure (in patients with chronic heart failure), feeling of coldness or numbness in the extremities, hypotension especially in patient with heart failure, asthenia (in patients with chronic heart failure), fatigue, postural hypotension, hepatitis, hypersensitivity.

These symptoms especially occur at the beginning of the therapy. They are generally mild and usually disappear within 1–2 weeks

Interactions with other medicines (*indicates serious):

- Applies only to chronic heart failure: *Class I antiarrhythmic drugs (e.g., quinidine, lidocaine, phenytoin, flecainide).
- Applies only to hypertension or angina pectoris: Class-I antiarrhythmic drugs.
- Applies to all indications: *Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type, *Centrally acting antihypertensive drugs such as clonidine and others (e.g., methyldopa) Calcium antagonists of the dihydropyridine type such as felodipine, and amlodipine, Class-III antiarrhythmic drugs (e.g., amiodarone), Topical beta-blockers (e.g., eye drops for glaucoma treatment), Parasympathomimetic drugs, Insulin and oral antidiabetic drugs, Anaesthetic agents, Digitalis glycosides, Non-steroidal anti-inflammatory drugs (NSAIMs), β-Sympathomimetic agents (e.g., isoprenaline, dobutamine), Sympathomimetics that activate both β- and α-adrenoceptors (e.g., norepinephrine, epinephrine), Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g., tricyclic antidepressants, barbiturates, phenothiazines, phosphodiesterase 5 inhibitors), Aminophylline/Theophylline.

Carvedilol

ATC code: C07AG02

Tablets, 3.125 mg, 6.25 mg, 12.5 mg, 25 mg LOU 4

Indications and dose

Adult

Hypertension: Initially 12.5 mg once daily for 2 days, then increased to 25 mg once daily, increased if necessary up to 50 mg daily in two divided doses; dose to be increased at intervals of at least 2 weeks and can be given as a single dose or in divided doses.

- **Elderly**: Initially 12.5 mg daily, initial dose may provide satisfactory control

Angina, oral: Initially 12.5 mg twice daily for 2 days, then increased to 25 mg twice daily; recommended maximum daily dose is 100 mg in two doses (50 mg twice daily)

Symptomatic chronic heart failure, in combination with diuretics, digoxin, or ACEIs, oral: Initially 3.125 mg twice daily, dose to be taken with food, then increased to 6.25 mg twice daily, then increased to 12.5 mg twice daily, then increased to 25 mg twice daily; dose should be increased at intervals of at least 2 weeks up to the highest tolerated dose; max. 25 mg twice daily in patients with severe heart failure or body weight less than 85 kg; max. 50 mg twice daily in patients over 85 kg

Left ventricular dysfunction after MI: Initial dose is 6.25 mg twice daily, increased after 3 to 10 days, if tolerated, to 12.5 mg twice daily and then to a target dose of 25 mg twice daily. A lower initial dose may be used in symptomatic patients.

Paediatric

Adjunct in heart failure, oral

Child 2–17 years: Initially 50 micrograms/kg twice daily (max. per dose 3.125 mg) for at least 2 weeks, then increased to 100 micrograms/kg twice daily for at least 2 weeks, then increased to 200 micrograms/kg twice daily, then increased if necessary up to 350 micrograms/kg twice daily (max. per dose 25 mg)

Contraindications: Hypersensitivity to carvedilol or to any of the excipients of Carvedilol, Heart failure belonging to the New York Heart Association Class IV of the heart failure classification with marked fluid retention or overload requiring IV inotropic treatment, chronic obstructive pulmonary disease with bronchial obstruction, clinically significant hepatic dysfunction, bronchial asthma, AV block, degree II or III (unless a permanent pacemaker is in place), severe bradycardia (<50 bpm), sick sinus syndrome (incl. sino-atrial block), cardiogenic shock, severe hypotension (systolic blood pressure below 85 mmHg), Prinzmetal's angina, untreated phaeochromocytoma, metabolic acidosis, severe peripheral arterial circulatory disturbances.

Hepatic impairment: Avoid in severe hepatic impairment.

Renal impairment: No dose adjustments necessary.

Pregnancy: Information on the safety of carvedilol during pregnancy is lacking. If carvedilol is used close to delivery, infants should be monitored for signs of alpha-blockade (as well as beta-blockade).

Breastfeeding: Carvedilol and its metabolites are excreted in breast milk and, therefore, mothers receiving carvedilol should not breastfeed

Adverse effects: Refer to Bisoprolol for adverse effects

Interactions with other medicines (*indicates serious): Chlorpromazine, artemether/lumefantrine, afatinib, * diltiazem, *verapamil, *amiodarone, *class I antiarrhythmics, methyldopa, *Dihydropyridines, e.g., amlodipine, nifedipine, Nitrates, Cardiac glycosides, e.g., *digoxin, antihypertensives, e.g., α1-receptor antagonists and medicines with antihypertensive adverse reactions such as barbiturates, phenothiazines, tricyclic antidepressants, vasodilating agents, alcohol, Ciclosporin, Antidiabetics including insulin, Clonidine, Inhalational anaesthetics. Non-Steroidal Antiinflamatory Drugs (NSAIMs), oestrogens, corticosteroids, Sympathomimetics with alpha-mimetic and beta-mimetic effects, Ergotamine.

Notes:

» Monitor renal function during dose titration in patients with heart failure who also have renal impairment, low blood pressure, ischaemic heart disease, or diffuse vascular disease.

Glyceryl Trinitrate

ATC code: C01DA02

Tablet, sublingual, 500 micrograms, LOU 4

Spray, sublingual, 400 micrograms/dose, LOU 4

Indications and dose

Adult

Prophylaxis of angina,

By sublingual administration using sublingual tablets: 1 tablet (500 micrograms), to be administered prior to activity likely to cause angina

By sublingual administration using aerosol spray (400 micrograms per 1 dose): 400–800 micrograms (1-2 sprays), to be administered under the tongue and then close mouth prior to activity likely to cause angina

Treatment of angina,

By sublingual administration using sublingual tablets: 1 tablet (500 micrograms), dose may be repeated at 5-minute intervals if required; if symptoms have not resolved after 3 doses, medical attention should be sought

By sublingual administration using aerosol spray (400 micrograms per 1 dose): 400–800 micrograms (1-2 sprays), to be administered under the tongue and then close mouth, dose may be repeated at 5-minute intervals if required; if symptoms have not resolved after 3 doses, medical attention should be sought

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: hypersensitivity to nitrates or any of the excipients, hypotension, hypovolaemia, hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis, marked anaemia, head trauma, increased intracranial pressure, cerebral haemorrhage, angle-closure glaucoma, concomitant use with phosphodiesterase 5 inhibitors.

Precautions: hypothyroidism, malnutrition, hypothermia, recent history of MI, cerebrovascular disease since symptoms may be precipitated by hypotension, patients with lung disease or cor pulmonale.

Hepatic impairment: No or insufficient data on the pharmacokinetics of this drug in hepatic impairment. Therefore, up titration should be done with caution.

Renal impairment: No or insufficient data on the pharmacokinetics of this drug in renal/hepatic impairment. Therefore, up titration should be done with caution.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: throbbing headache, vertigo, dizziness (if these three effects persist after relief of angina, they may be minimised by removing the tablet before it has completely dissolved), flushing, postural hypotension (especially at initiation and dose increase), tachycardia, paradoxical bradycardia. Local burning or tingling sensation under the tongue may occur.

Interactions with other medicines (*indicates serious): *Phosphodiesterase type 5 inhibitors (e.g., sildenafil, tadalafil), agents with hypotensive effects (e.g., vasodilators, antihypertensives, beta-blockers, CCBs and neuroleptics, tricyclic antidepressants), alcohol, ergot alkaloids, antimuscarinics, dapsone, prilocaine. Nitrate tolerance may occur when used with long-acting nitrates.

Notes

» Hypotension and syncope can be a problem with use of nitrates in the elderly. Patients should be advised to sit down whenever possible when taking sublingual glyceryl trinitrate.

Isosorbide Dinitrate

ATC code: C01DA08

Tablet, 20 mg, LOU 4

Tablet (Sublingual), 5mg, LOU 4

Indications and dose

Adult

Prophylaxis and treatment of angina, oral: 20–120 mg daily in 2-3 divided doses (8-12 hourly).

By sublingual tablet (prophylaxis): 2.5-5 mg 15 minutes before performing activities likely to cause angina.

By sublingual tablet (treatment): 2.5-5 mg; may be repeated every 5-10 minutes; not to exceed 3 doses in 15-30 minutes.

Left ventricular failure/congestive cardiac failure, oral: 30–60 mg daily in divided doses, increased if necessary up to 240 mg daily in divided doses.

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: See Glyceryl trinitrate contraindications.

Precautions: hypothyroidism, malnutrition, hypothermia, recent history of MI, closed angle glaucoma, G6PD deficiency, patients with seriously damaged myocardia.

Hepatic impairment: No or insufficient data on the pharmacokinetics of this drug in hepatic impairment. Therefore, up titration should be done with caution.

Renal impairment: No or insufficient data on the pharmacokinetics of this drug in renal impairment. Therefore, up titration should be done with caution.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: peripheral oedema, throbbing headache (nitrate headache), flushing, dizziness, postural hypotension, tachycardia, paradoxical bradycardia, angioedema, angle closure glaucoma, hypoventilation, hypoxia, pituitary haemorrhage, SJS

Interactions: Refer to Glyceryl trinitrate interactions

Notes:

» The use of isosorbide dinitrate (ISDN) tablets in severe congestive cardiac failure should be regarded as an adjunctive therapy to more conventional treatment (e.g., cardiac glycosides, diuretics).

» Patients taking ISDN for the long-term management of angina may often develop tolerance to the antianginal effect, this can be avoided by giving the second of 2 daily doses of longer-acting oral presentations after an 8-hour rather than a 12-hour interval, thus ensuring a nitrate-free interval each day. Dosage should be gradually increased to minimise the possibility of nitrate headache and/or tolerance.

Trimetazidine

ATC code: C01EB15

Tablet (m/r), 35 mg, LOU 4

Indications and dose

Long-term treatment of angina pectoris in combination with other medicines

Adult

Angina, oral: 35 mg twice daily, in the morning and evening with meals

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Hypersensitivity to the active substance or to any of the excipients, Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders, severe renal impairment (CrCl < 30 mL/min).

Precautions: close-angle glaucoma, Trimetazidine can cause or worsen symptoms such as trembling, rigid posture, slow movements and a shuffling, unbalanced walk, especially in elderly patients (increased falls risk).

Hepatic impairment: No or insufficient data on the pharmacokinetics of this drug in hepatic impairment. Therefore, up titration should be done with caution.

Renal impairment: Do not use if CrCl <30 mL/min.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Dizziness, headache, GI disturbance, rash, asthenia, pruritus, urticarial, agranulocytosis, thrombocytopenia, thrombocytopenic purpura, hepatitis.

Interactions with other medicines: No drug interactions have been identified.

Notes:

» Athletes: This medicine contains an active substance which may give a positive reaction in doping tests.

14.2. Antiarrhythmic Medicines

Adenosine

ATC code: C01EB10

Injection, 6 mg/2 mL, LOU 6

Indications and dose

Adult

Rapid reversal of paroxysmal supraventricular tachycardias to sinus rhythm, including those associated with accessory conducting pathways (e.g., Wolff-Parkinson-White syndrome); used to aid diagnosis of broad or narrow, complex supraventricular tachycardias, by rapid IV injection

» *Patients without heart transplant (cardiac monitoring required):* Initially 6 mg, administer into central or large peripheral vein and give over 2 seconds followed by rapid saline flush, followed by 12 mg after 1–2 minutes if required, then 12 mg after 1–2 minutes if required; increments should not be given if high-level AV block develops at any particular dose

» *Patients with a heart transplant:* Initially 3 mg, administer into a central or large peripheral vein and give over 2 seconds then give a rapid saline flush, followed by 6 mg after 1–2 minutes if required, then 12 mg after 1–2 minutes if required; patients with a heart transplant are very sensitive to the effects of adenosine

Paediatric

Termination of supraventricular tachycardias, including those associated with accessory conducting pathways (e.g., Wolff-Parkinson-White syndrome), diagnosis of supraventricular arrhythmias, by rapid IV injection

Neonate: Initially 150 micrograms/kg, then increased in steps of 50–100 micrograms/kg every 1–2 minutes (max. per dose 300 micrograms/kg) if required; dose to be repeated until tachycardia terminated, or maximum single dose given

Child 1–11 months: Initially 150 micrograms/kg, then increased in steps of 50–100 micrograms/kg every 1–2 minutes (max. per dose 500 micrograms/kg) if required; dose to be repeated until tachycardia terminated, or maximum single dose given

Child 1–11 years: Initially 100 micrograms/kg, then increased in steps of 50–100 micrograms/kg every 1–2 minutes (max. per dose 12 mg) if required; dose to be repeated until tachycardia terminated, or maximum single dose given

Child 12–17 years: Initially 3 mg, followed by 6 mg after 1–2 minutes if required, followed by 12 mg after 1–2 minutes if required; in some children over 12 years, 3 mg dose ineffective (e.g., if a small peripheral vein is used for administration) and higher initial dose sometimes used, however, those with heart transplant are very sensitive to the effects of adenosine and should not receive higher initial doses.

Contraindications: Asthma, chronic obstructive lung disease, decompensated heart failure, long QT syndrome, second- or third-degree AV block and sick sinus syndrome

(Unless pacemaker fitted), severe hypotension, known hypersensitivity to adenosine or to any of the excipients, concomitant administration of adenosine with dipyridamole (if this combination must be used then the dose of adenosine should be greatly reduced).

Precautions: used with caution in patients with left main coronary stenosis, uncorrected hypovolemia, stenotic valvular heart disease, left to right shunt, pericarditis or pericardial effusion, QT-interval prolongation, autonomic dysfunction or stenotic carotid artery disease with cerebrovascular insufficiency, recent MI, severe heart failure, or in patients with minor conduction defects (first degree A-V block, bundle branch block), atrial fibrillation or flutter and especially in those with an accessory by-pass tract. Dose should be reduced in patients with heart transplant.

Hepatic Impairment: Since neither the kidney nor the liver are involved in the degradation of exogenous adenosine, adenosine injection's efficacy should be unaffected by hepatic or renal insufficiency.

Renal Impairment: Since neither the kidney nor the liver are involved in the degradation of exogenous adenosine, adenosine injection's efficacy should be unaffected by hepatic or renal insufficiency.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: bradycardia, sinus pause, skipped beats, atrial extrasystoles, transient Atrio-Ventricular block, ventricular excitability disorders such as ventricular extrasystoles, non-sustained ventricular tachycardia, asystole/cardiac arrest (sometimes fatal especially in patients with underlying ischemic heart disease/cardiac disorder), flushing, headache, dizziness, light-headedness, paraesthesia, dyspnea, throat and abdominal discomfort, nausea, dry mouth, nervousness, burning sensation, chest pain or pressure, feeling of thoracic constriction/oppression, hypotension, coronary steal, atrial fibrillation can be

initiated or cause decompensation in the presence of pre-excitation. Minor Adverse effects are usually transient, lasting less than a minute because of adenosine's very short half-life.

Interactions with other medicines (*indicates serious): *Dipyridamole, *Aminophylline, *theophylline and other *xanthines, including food and drinks containing xanthines (tea, coffee, chocolate and cola), digoxin, verapamil.

Amiodarone

ATC code: C01BD01

Injection, 50 mg/mL as HCl (3 mL), LOU 5

Tablet, 100 mg, 200 mg as HCl, LOU 4

Indications and dose

Ventricular and supraventricular arrhythmias (particularly when other drugs are ineffective or contraindicated), including arrhythmias associated with Wolff-Parkinson-White syndrome

Adult

Arrhythmias, oral: 200 mg 3 times a day for 1 week, then reduced to 200 mg twice daily for a further week, followed by maintenance dose, usually 200 mg daily or the minimum dose required to control arrhythmia

Arrhythmias, by IV infusion: Initially 5 mg/kg, to be given over 20–120 minutes with ECG monitoring; subsequent infusions given if necessary, according to response; maximum 1.2 g per day

Ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation (for cardiopulmonary resuscitation), initially by IV injection: Initially 300 mg, dose to be considered after administration of epinephrine; dose should be given from a pre-filled syringe or diluted in 20 mL glucose 5%, then (by IV injection) 150 mg if required, followed by IV infusion 900 mg/24 hours

Paediatric

Supraventricular and ventricular arrhythmias (initiated in hospital or under specialist supervision, oral

Neonate: Initially 5–10 mg/kg twice daily for 7–10 days , then reduced to 5–10 mg/kg daily.

Child 1 month–11 years: Initially 5–10 mg/kg twice daily (max. per dose 200 mg) for 7–10 days, then reduced to 5–10 mg/kg once daily; maximum 200 mg per day

Child 12–17 years: 200 mg 3 times a day for 1 week, then 200 mg twice daily for 1 week, then usually 200 mg daily adjusted according to response

Supraventricular and ventricular arrhythmias (initiated in hospital or under specialist supervision, initially by IV infusion

Neonate*: Initially 5 mg/kg, then (*By IV infusion*) 5 mg/kg every 12–24 hours, dose to be given over 30 minutes

Child: Initially 5–10 mg/kg, dose to be given over 20 minutes to 2 hours, then (by continuous IV infusion) 300 micrograms/kg/hour, adjusted according to response (by continuous IV infusion), increased if necessary up to 1.5 mg/kg/hour; maximum 1.2 g per day

NB: *Injections containing benzyl alcohol should be avoided in neonates.

Ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation (for cardiopulmonary resuscitation), initially by IV injection

Neonate: 5 mg/kg to be given over at least 3 minutes

Child: 5 mg/kg (max. per dose 300 mg) to be given over at least 3 minutes.

Contraindications: Avoid in severe conduction disturbances (unless pacemaker fitted), avoid in sinus node disease (unless pacemaker fitted), Hypersensitivity to amiodarone, iodine and any of the excipients, sino-atrial heart block (except in cardiac arrest), sinus bradycardia (except in cardiac arrest), thyroid dysfunction, combination of amiodarone with drugs which may induce Torsades de Pointes (see interactions section for details), pregnancy and breastfeeding.

Specific contraindication with IV use: Avoid bolus injection in cardiomyopathy, congestive heart failure, circulatory collapse, severe arterial hypotension, severe respiratory failure.

Precautions: Acute porphyrias, conduction disturbances (in excessive dosage), elderly, heart failure, hypokalaemia, severe bradycardia (in excessive dosage). Treatment should be discontinued in case of onset of 2nd or 3rd degree A-V block, sino-atrial block or bifascicular block Before surgery, the anaesthetist should be informed that the patient is taking amiodarone. Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin, and peripheral nervous system. Because these reactions may be delayed, patients on long-term treatment should be carefully supervised. As undesirable effects are usually dose-related, the minimum effective maintenance dose should be given. With IV use: moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage), severe hepatocellular toxicity

Hepatic Impairment: No or insufficient data on the pharmacokinetics of this drug in hepatic impairment. Therefore, up titration should be done with caution. Amiodarone can cause hepatotoxicity therefore patients' liver function should be monitored closely.

Renal Impairment: No or insufficient data on the pharmacokinetics of this drug in renal/hepatic impairment. Therefore, up titration should be done with caution.

Pregnancy: Possible risk of neonatal goitre, use only if no alternative.

Breastfeeding: Avoid, present in milk in significant amounts, theoretical risk of neonatal hypothyroidism from release of iodine.

Adverse effects:

Arrhythmias, hepatic disorders, nausea, respiratory disorders, skin reactions, Bronchospasm (in patients with severe respiratory failure), headache, idiopathic intracranial hypertension, nerve disorders, SIADH, Angioedema, confusion, delirium, pancreatitis, SCARs. With oral use: Constipation, corneal deposits, hypothyroidism, movement disorders, photosensitivity reaction, sleep disorders, taste altered, vomiting.

With parenteral use: Hypotension (following rapid injection) Corneal Microdeposits, thyroid dysfunction, hepatotoxicity, pulmonary toxicity (pneumonitis).

Interactions with other medicines (*indicates serious): *Drugs inducing Torsade de Pointes or prolonging QT, e.g., *Class Ia anti-arrhythmic drugs (e.g., quinidine, procainamide), *Class III anti-arrhythmic drugs (e.g., sotalol), *co-trimoxazole, *pentamidine injection, *some anti-psychotics (e.g., *chlorpromazine,* fluphenazine,* haloperidol,* amisulpiride),* lithium and* tricyclic anti-depressants, e.g., (* amitriptyline), *anti-malarials, e.g., (* quinine, *mefloquine), *erythromycin, * clarithromycin,* fluoroquinolones e.g., *moxifloxacin, *Beta blockers, *calcium channel inhibitors (*diltiazem, *verapamil), *Stimulant laxatives, diuretics, systemic corticosteroids, tetracosactide, amphotericin, general anaesthesia, high dose oxygen therapy, *ticagrelor. Amiodarone and/or its metabolite, desethylamiodarone, may increase exposure to substrates of CYP1A1, CYP1A2, CYP3A4 (e.g., *ciclosporin, *simvastatin, lidocaine, * tacrolimus, sildenafil, fentanyl, midazolam, ergotamine and *colchicine), CYP2C9 (e.g., *warfarin, *phenytoin), CYP2D6 (e.g., flecainide) and Pglycoprotein (e.g., *digoxin, dabigatran). Amiodarone levels may be increased by CYP3A4 inhibitors, e.g., (grapefruit juice, ketoconazole, *ritonavir) and CYP2C8 inhibitors, e.g., clopidogrel.

Notes:

- Monitoring requirements, before starting amiodarone, it is recommended to perform an ECG, chest X-ray, serum potassium measurement, thyroid and liver function tests. Monitoring of ECG is recommended during IV treatment.
- Amiodarone may increase the defibrillation threshold and/or pacing threshold in patients with an implantable cardioverter defibrillator or a pacemaker, which may adversely affect the efficacy of the device. Regular tests are recommended to ensure the proper function of the device after initiation of treatment or change in dose.
- Amiodarone has a long half-life, there is potential for Interactions with other medicines to occur for several weeks (or even months) after treatment with it has been stopped.

Atropine

ATC code: A03BA01

Injection, 1 mg (as sulphate) in 1-mL amp, LOU 4

Indications and dose

Adults

Symptomatic bradycardia due to acute over dosage of beta-blockers, intravenous injection: 0.5–1.2 mg, repeat doses may be necessary.

Intra-operative bradycardia, intravenous injection: 300–600 mg micrograms, larger doses may be used in emergencies.

Excessive bradycardia associated with beta-blocker use, intravenous injection: 0.6–2.4 mg in divided doses (max. per dose 600 micrograms)

Bradycardia following myocardial infarction (particularly if complicated by hypotension), intravenous injection: 500 micrograms every 3–5 minutes; maximum 3 mg per course.

Paediatric

Symptomatic bradycardia due to acute massive overdosage of beta-blockers, intravenous injection: 0.02 mg/kg (max. per dose 1.2 mg), repeat doses may be necessary.

Intra operative Bradycardia, intravenous injection

Neonate: 10–20 micrograms/kg

1 month – 11 years: 10–20 micrograms/kg

12–17 years: 300–600 micrograms, larger doses may be used in emergencies

Contraindications: *(Refer to section 1.3.)*

Precautions: *(Refer to section 1.3.)*

Hepatic and renal impairment: *(Refer to section 1.3.)*

Adverse effects: *(Refer to section 1.3.)*

Interactions with other medicines: *(Refer to section 1.3.)*

Bisoprolol

See Bisoprolol in section 14.1 Antianginal medicines

Carvedilol

See Carvedilol in section 14.1 Antianginal medicines

Digoxin

ATC code: C01AA05

Oral liquid, 50 micrograms/mL, LOU 4

Tablet, 125 micrograms, 250 micrograms, LOU 4

Indications and dose

Supraventricular arrhythmias, particularly atrial fibrillation, heart failure

Adult

Rapid digitalisation for atrial fibrillation or flutter, oral: 0.75–1.5 mg in divided doses, dose to be given over 24 hours

- **Elderly:** Reduce dose

Maintenance, for atrial fibrillation or flutter, oral: 125–250 micrograms daily, dose according to renal function and initial loading dose

- **Elderly**: Reduce dose

Atrial fibrillation, oral: Initially 1–1.5 mg in divided doses over 24 hours for rapid digitalization (or 250 micrograms once or twice daily if digitalization less urgent) followed by 62.5–500 micrograms daily

(higher dose may be divided), according to renal function and heart rate response; usual maintenance dose, 125 micrograms

» **Elderly**: Daily dose more appropriate

Heart failure, oral: Initially 1–1.5 mg in divided doses over 24 hours for rapid digitalization (or 250 micrograms once or twice daily if digitalization less urgent), followed by 62.5–500 micrograms daily (higher dose may be divided), according to renal function and heart rate response; usual maintenance dose, 125 micrograms daily

» **Elderly**: Lower dose more appropriate

Emergency control of atrial fibrillation, by IV infusion: 0.75–1 mg; give over at least 2 hours

Heart failure, emergency loading dose, by IV infusion: 0.75–1 mg; give over at least 2 hours

Paediatric

Supraventricular arrhythmias, chronic heart failure, oral

Neonate under 1.5 kg: Initially 25 micrograms/kg in 3 divided doses for 24 hours then 4–6 micrograms/kg/day in 1–2 divided doses

Neonate 1.5–2.5 kg: Initially 30 micrograms/kg in 3 divided doses for 24 hours then 4–6 micrograms/kg/day in 1–2 divided doses

Neonate over 2.5 kg or **child under 2 years:** initially 45 micrograms/kg in 3 divided doses for 24 hours then, 10 micrograms/kg/day in 1–2 divided doses

Child 2–5 years: Initially 35 micrograms/kg in 3 divided doses for 24 hours then, 10 micrograms/kg/day in 1–2 divided doses

Child 5–10 years: Initially 25 micrograms/kg (maximum 750 micrograms) in 3 divided doses for 24 hours then, 6 micrograms/kg/day (maximum 250 micrograms daily) in 1–2 divided doses

Child over 10 years: Initially 0.75–1.5 mg in 3 divided doses for 24 hours then 62.5–250 micrograms/daily in 1–2 divided doses (higher doses may be necessary)

Supraventricular arrhythmias, chronic heart failure, IV infusion

Neonate under 1.5 kg: initially 20 micrograms/kg in three divided doses for 24 hours then 4–6 micrograms/kg/day in 1–2 divided doses

Neonate 1.5–2.5 kg: initially 30 micrograms/kg in three divided doses for 24 hours then 4–6 micrograms/kg/day in 1–2 divided doses

Neonate over 2.5 kg or **child under 5 years:** Initially 35 micrograms/kg in 3 divided doses for 24 hours then, 10 micrograms/kg/day in 1–2 divided doses

Child 5–10 years: Initially 25 micrograms/kg (maximum 500 micrograms) in 3 divided doses for 24 hours then, 6 micrograms/kg/day (maximum 250 micrograms daily) in 1–2 divided doses

Child over 10 years: Initially 0.5–1 mg in 3 divided doses for 24 hours then 62.5–250 micrograms daily in 1–2 divided doses (higher doses may be necessary)

Contraindications: hypertrophic obstructive cardiomyopathy (unless also severe heart failure), Wolff-Parkinson-White syndrome or other accessory pathway, particularly if accompanied by atrial fibrillation (although can be used in infancy), ventricular tachycardia or fibrillation, intermittent complete heart block, second-degree atrioventricular block, myocarditis, Constrictive pericarditis (unless to control atrial fibrillation or improve systolic dysfunction —but use with caution).

Precautions: recent MI, sick sinus syndrome, severe pulmonary disease, thyroid disease, the elderly (reduce dose), avoid rapid IV administration (nausea and increased risk of arrhythmias), Risk of digitalis toxicity with Hypercalcaemia, hypokalaemia, hypomagnesaemia, hypoxia.

Hepatic Impairment: Hepatic impairment has little effect on digoxin clearance.

Renal Impairment: Reduce dose. Monitor plasma-digoxin concentration in renal impairment.

Pregnancy: May need dosage adjustment as dosage may be less predictable in pregnant women. Adverse foetal effects have been reported in mothers with digitalis toxicity.

Breastfeeding: Amount excreted in breastmilk too small to be harmful.

Adverse effects: usually only associated with high doses, GI disturbances including anorexia, nausea, vomiting, diarrhoea, and abdominal pain, visual disturbances (blurred vision or xanthopsia), headache, fatigue, drowsiness, confusion, dizziness, delirium, hallucinations, depression, arrhythmias (especially with digoxin toxicity), heart block, conduction disorder, bigeminy, trigeminy, PR prolongation, sinus bradycardia, intestinal ischaemia, GI necrosis, gynaecomastia on long-term use, thrombocytopenia, rash (Skin rashes of urticarial or scarlatiniform character may be accompanied by pronounced eosinophilia), Nervous system disorder

Interactions with other medicines (*indicates serious): *Ciclosporin, flecainide, *propafenone, *betablockers (e.g., carvedilol), adenosine, aminoglycosides (e.g., gentamycin), antithyroid agents, CCBs (Non dihydropyridine i.e. *verapamil and *diltiazem), Azole antifungals (e.g., *itraconazole, *ketoconazole, *indomethacin), colchicine, fluoxetine, ivabradine, *Nonsteroidal antiinflamatory drugs (e.g., indomethacin), ranolazine, *spironolactone, ticagrelor, *amiodarone, canagliflozin, prazosin, quinidine, *macrolide antibiotics (e.g., erythromycin and clarithromycin), tetracycline, *quinine, *mefloquine, *mirabegron, atorvastatin, *ritonavir/ritonavir containing regimens, telmisartan, lapatinib, phenytoin, Penicillamine, *St John's Wort, *sucralfate, *Drugs that reduce serum potassium (e.g., loop diuretics e.g., furosemide, acetazolamide, ampoteracin B), neuromuscular blocking drugs (e.g., suxamethonium, pancuronium),

Notes:

» For plasma-digoxin concentration assay, blood should be taken at least 6 hours after a dose. When switching from IV to oral route may need to increase dose by 20–33% to maintain the same plasma-digoxin concentration. Dose may need to be reduced if digoxin (or another

cardiac glycoside) has been given in the preceding 2 weeks.

» Monitor serum electrolytes and renal function. Toxicity increased by electrolyte disturbances. Digoxin therapy in conjunction with electrolyte abnormalities may lead to malignant arrhythmias. Correct K+, Mg+, and Ca2+ for patients on digoxin.

Epinephrine (Adrenaline)

ATC code: C01CA24

Injection: 1 mg/mL (1-mL amp), LOU 4

Indications and dose

Adults

By:

Cardiopulmonary resuscitation (specialist use only), slow intravenous injection: 1 mg every 3–5 minutes as required, a 1 in 10 000 (100 micrograms/mL) solution is recommended

Control of bradycardia in patients with arrhythmias after myocardial infarction, if there is a risk of asystole, or if the patient is unstable and has failed to respond to atropine, intravenous infusion: *2–10 micrograms*/minute, adjusted according to response

Paediatric

Cardiopulmonary resuscitation (specialist use only), slow intravenous injection: 10 micrograms/kg every 3–5 minutes (max. per dose 1 mg) as required, a 1 in 10 000 (100 micrograms/mL) solution is recommended, suitable syringe to be used for measuring small volume.Acute hypotension, continuous intravenous infusion

Neonate: Initially 100 nanograms/kg/minute, adjusted according to response, higher doses up to 1.5 micrograms/kg/minute have been used in acute hypotension.

Child: *Initially 100 nanograms/kg/minute, adjusted according to response,* higher doses up to 1.5 micrograms/kg/minute have been used in acute hypotension

Contraindications: *(Refer to section 4)*

Precautions: *(Refer to section 4)*

Hepatic and renal impairment: *(Refer to section 4)*

Adverse effects: *(Refer to section 4)*

Interactions with other medicines: *(Refer to section 4)*

Lignocaine (Lidocaine) hydrochloride

ATC code: C01BB01

Injection, preservative free 2% (HCl) in vial, LOU 5

Indications and dose

Adult

Cardiopulmonary resuscitation (as an alternative if amiodarone is not available), intravenous injections: : 1 mg/kg, do not exceed 3 mg/kg over the first hour

Ventricular arrhythmias, especially after myocardial infarction in patients without circulatory impairment, intravenous infusion: Initially 100 mg, to be given as a bolus dose over a few minutes, followed immediately by 4 mg/minute for 30 minutes, then 2 mg/minute for 2 hours, then 1 mg/minute.

The initial intravenous injection of 100mg can be repeated if necessary, once or twice at intervals of not less than 10 minutes if an intravenous infusion is not immediately available.

Ventricular arrhythmias, especially after myocardial infarction in lighter patients or those whose circulation is severely impaired, intravenous infusion: Initially *by intravenous injection 50 mg, to be given as a bolus dose over a few minutes, followed immediately by 4 mg/minute for 30 minutes, then (by intravenous infusion) 2 mg/minute for 2 hours, then 1 mg/minute.*

The initial intravenous injection of 50mg can be repeated if necessary, once or twice at intervals of not less than 10 minutes.

Paediatric

Ventricular arrhythmias, Pulseless ventricular tachycardia, Ventricular fibrillation

Initially by intravenous injection, or by intraosseous Injection

Neonate: Initially 0.5–1 mg/kg, followed immediately by (by intravenous infusion) 0.6–3 mg/kg/hour, alternatively (by intravenous injection or by intraosseous injection) 0.5–1 mg/kg repeated at intervals of not less than 5 minutes if infusion is not immediately available following initial injection, until infusion can be initiated; maximum 3 mg/kg per course.

Child 1 month–11 years: Initially 0.5–1 mg/kg, followed immediately by (by intravenous infusion) 0.6–3 mg/kg/hour, alternatively (by intravenous injection or by intraosseous injection) 0.5–1 mg/kg repeated at intervals of not less than 5 minutes if infusion is not immediately available following initial injection, until infusion can be initiated; maximum 3 mg/kg per course.

Child 12–17 years: Initially 50–100 mg, followed by (by intravenous infusion) 120 mg, dose to be given over 30 minutes, then (by intravenous infusion) 240 mg, dose to be given over 2 hours, then (by intravenous infusion) 60 mg/hour, reduce dose further if infusion is continued beyond 24 hours, if infusion not immediately available following initial injection, the initial injection dose may be repeated at intervals of not less than 5 minutes (to a maximum 300mg dose in 1 hour) until infusion can be initiated.

Contraindications:

» Hypersensitivity to the active substance, to anaesthetics of the amide type.

» Complete heart block

» Hypovolaemia

Precautions: Acid-base balance disorders, hypoxia and hypokalemia should be corrected before treatment with intravenous lidocaine in patients who require large doses of antiarrhythmic agents

Use with caution in patients with heart failure,

epilepsy, myasthenia gravis, bradycardia, or respiratory depression.

Interactions with other medicines (*indicates serious): Cerum concentration of Lidocaine can be increased when it is combined with cimetidine or propranolol- dosage reduction of lidocaine is required.

Increase in serum levels of lidocaine may also occur with anti-viral agents (*amprenavir, atazanavir, darunavir, lopinavir)

Lidocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics (e.g., anti-arrhythmics, such as mexiletine), since the systemic toxic effects are additive.

Specific interaction studies with lidocaine and class III anti-arrhythmic drugs (e.g., amiodarone) have not been performed, but caution is advised.

Cardiovascular collapse has been reported following the use of bupivacaine in patients on treatment with *verapamil and* timolol; Lidocaine is closely related to bupivacaine

Risk of aggravated ventricular arrhythmia in patients treated concurrently with antipsychotics which prolong or may prolong the QT interval (***pimozide, sertindole, adrenaline olanzapine, quetiapine, zotepine***), prenylamine (if accidently injected intravenously) or 5HT3 antagonists (*tropisetron, dolasetron*). Concomitant use of *quinupristin/dalfopristin may increase lidocaine levels therefore this should be avoided.

There may be an increased risk of enhanced and prolonged neuromuscular blockade in patients treated concurrently with muscle relaxants (e.g. suxamethonium).

Notes:

» ECG monitoring and specialist advice for Infusion. Reduce the concentration if additional infusion is needed after 24 hours. The duration of action for lignocaine lasts for 15–20 minutes after an intravenous injection

See section 1.2.3 for additional details.

Verapamil

ATC code: C08DA01

Tablet (modified release), 120 mg (as HCl), LOU 4

Tablet (immediate release), 40 mg (as HCl), LOU 4

Indications and dose

Adult

Angina, oral: immediate release (i/r) tablet, 80–120 mg 3 times daily (120 mg 3 times daily usually required in Prinzmetal angina); some patients with angina of effort may respond to 80 mg three times daily, but this lower dose is not likely to be effective in angina at rest or Prinzmetal's variant angina.

NB: Modified-release preparations may be given in doses of up to 480 mg daily in two divided doses.

Hypertension, oral: i/r tablet, initial oral dose is 240 mg daily, in 2 or 3 divided doses, adjusted according to response, doses of up to 480 mg daily in two divided doses have been used.

NB: Modified-release preparations may be given in similar daily doses.

Supraventricular arrhythmias: i/r tablets: 40–120 mg 3 times a day

Secondary prevention of MI: Modified-release preparation, started at least 1 week after acute infarction (in patients without heart failure), in a dose of 360 mg daily in divided doses either as 240 mg mane and 120 mg nocte or 120 mg three times a day

Paediatric

Prophylaxis of supraventricular arrhythmias or for hypertension, oral, i/r tablets under expert advise

Child 1 year up to 23 months: 20 mg two or three times a day

Child 2 years and over: 40 to 120 mg two or three times daily

Contraindications: Acute porphyrias, hypotension, bradycardia, second- and third-degree atrioventricular block, sinoatrial block, sick sinus syndrome, cardiogenic shock, history of heart failure or significantly impaired left ventricular function (even if controlled by therapy), atrial flutter or fibrillation complicating Wolff-Parkinson-White syndrome, bradycardia, combination with ivabradine, combination with betablockers in patients with poor ventricular function.

Precautions: first-degree atrioventricular block, acute phase of MI (avoid if bradycardia, hypotension, or left ventricular failure present), diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy), Sudden withdrawal might exacerbate angina.

Hepatic impairment: Oral dose may need to be reduced, up titrate with caution.

Renal impairment: No or insufficient data on the pharmacokinetics of this drug in renal impairment. Therefore, up titration should be done with caution.

Pregnancy: May reduce uterine blood flow with foetal hypoxia. Avoid in first trimester unless absolutely necessary. May inhibit labour.

Breastfeeding: Amount too small to be harmful. Use only is essential.

Adverse effects: GI disturbance, headache, dizziness, fatigue, and ankle oedema, allergic reactions including pruritus, urticaria, angioedema, and erythema multiforme (SJS), myalgia, arthralgia, paraesthesia, erythromelalgia, increased prolactin concentration, gynaecomastia and gingival hyperplasia on long-term treatment, hypotension, heart failure, bradycardia, heart block, and asystole (due to negative inotropic effect) with high doses. IV administration, cardiac arrest, hepatic impairment, myocardial contractility reduced, seizure

Interactions with other medicines (*indicates serious): *atenolol, *carbamazepine, *ciclosporin, *digoxin, *erythromycin, *halothane, *ketamine, *lidocaine, *nitrous oxide, methyldopa, lithium, ibuprofen, hydrocortisone, glyceryltrinitrate, amitriptyline, amiloride, diazepam, enalapril, isosorbide dinitrate, furosemide, chlorpromazine, oral contraceptives,

dexamethasone, hydralazine, hydrochlorthiazide, *ivabradine, acetylsalicylic acid, grapefruit juice.

14.3. Antihypertensive Medicines

14.3.1. Angiotensin-Converting Enzyme Inhibitors (ACEIs)

Enalapril

ATC code: C09AA02

Tablet (scored), 5 mg as hydrogen maleate, LOU 3

Tablet (scored), 10 mg as hydrogen maleate, LOU 3

Tablet (scored), 20 mg as hydrogen maleate, LOU 3

Indications and dose

Adults

Hypertension, oral: Initially 5 mg once daily, lower if used in addition to a diuretic or in renal impairment; give first dose at bedtime; increase if necessary; usual maintenance dose 20 mg once daily; maximum 40 mg once daily

Heart failure and prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction, oral: Initially 2.5 mg daily under close medical supervision, increased over 2–4 weeks to usual maintenance dose of 20 mg daily, either as a single dose or in 2 divided doses; maximum 40 mg daily.

Paediatric

Hypertension and heart failure, oral

Neonate: Initially 10 micrograms/kg once daily, increased as necessary up to 500 micrograms/kg daily in 1–3 divided doses; monitor blood pressure and urine output carefully for at least 2 hours following first dose and during dose escalation until blood pressure is stable.

Child 1 month–11 years (under expert supervision): Initially 100 micrograms/kg once daily, monitor blood pressure carefully for 1–2 hours, then increase if necessary up to 1 mg/kg daily in 1–2 divided doses

Child 12–17 years (under expert supervision) (body weight up to 50 kg): Initially 2.5 mg once daily, monitor blood pressure carefully for 1–2 hours, maintenance 10–20 mg daily in 1–2 divided doses

Child 12–17 years (under expert supervision) (body weight 50 kg and above): Initially 2.5 mg once daily, monitor blood pressure carefully for 1–2 hours, maintenance 10–20 mg daily in 1–2 divided doses, maximum 40 mg.

Contraindications: hypersensitivity to ACEIs (including angioedema), renovascular disease, pregnancy.

Precautions: concomitant use of diuretics (initiate at low dose and monitor closely), hypotension with first doses, especially in patients on diuretics, on a low-sodium diet, on dialysis, if dehydrated, or with heart failure, peripheral vascular disease or generalized atherosclerosis (risk of clinically silent renovascular disease), severe or symptomatic aortic stenosis (use with great care), possibly increased risk of agranulocytosis in collagen vascular disease, history of idiopathic or hereditary angioedema (use with care or avoid)

Hepatic impairment: Enalapril is a prodrug and requires close monitoring in patients with hepatic impairment.

Renal impairment: Monitor renal function before and during treatment.

Pregnancy No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: Avoid in first few weeks after delivery, particularly in preterm infants— risk of profound neonatal hypotension, can be used in mothers breastfeeding older infants if essential but monitor infant's blood pressure.

Adverse effects: dizziness, headache, less commonly, nausea, hypotension (severe in rare cases), dry cough, fatigue, asthenia, muscle cramps, rash, and renal impairment, GI disturbance, peptic ulcer, glossitis, stomatitis, ileus, pancreatitis, liver damage, chest pain, palpitations, arrhythmias, Raynaud syndrome, angioedema, bronchospasm, rhinorrhoea, dry mouth, sore throat, pulmonary infiltrates, paraesthesia, vertigo, nervousness, depression, confusion, drowsiness, insomnia, dream abnormalities, pruritus, urticaria, alopecia, flushing, impotence, gynaecomastia, SJS, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus, tinnitus, and blurred vision, electrolyte disturbances and hypersensitivity-like reactions (including fever, myalgia, arthralgia, eosinophilia, and photosensitivity), hypoglycaemia.

Interactions with other medicines (*indicates serious): *acetazolamide, acetylsalicylic acid, alcohol, *amiloride, amlodipine, antacids, atenolol, chlorpromazine, *ciclosporin, oral contraceptives, dexamethasone, diazepam, *furosemide, glibenclamide, glyceryl trinitrate, haloperidol, heparin, hydralazine, *hydrochlorthiazide, hydrocortisone, *lithium, *potassium salts, *spironolactone, metformin, prednisolone, verapamil, nifedipine.

Note:

» Anaphylactoid reactions: Avoid enalapril during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein (LDL) apheresis with dextran sulphate, also withhold before desensitization with wasp or bee venom.

14.3.2. Angiotensin Receptor Blockers (ARBs)

Losartan

ATC code: C09CA01

Tablet (scored), 50 mg, LOU 3

Indications and dose

Adult

Hypertension, oral:

» 18–75 years: Initially 50 mg once daily for

several weeks, then increase if necessary to 100 mg once daily

» 76 years and over: Initially 25 mg once daily for several weeks, then increase if necessary to 100 mg once daily

Hypertension with intravascular volume depletion, oral, 18–75 years: Initially 25 mg once daily for several weeks, then increase if necessary up to 100 mg once daily

Chronic heart failure when ACEIs are unsuitable or contraindicated, oral: Initially 12.5 mg once daily, increase if tolerated up to 150 mg once daily; doses to be increased at weekly intervals

Diabetic nephropathy in type 2 diabetes mellitus, oral

» 18–75 years: Initially 50 mg once daily for several weeks, then increase if necessary to 100 mg once daily

» 76 years and over: Initially 25 mg once daily for several weeks, then increase if necessary to 100 mg once daily

Paediatric

Hypertension

Child 6–17 years (under expert supervision) (body weight 20–49 kg): Initially 700 micrograms/kg once daily (max. per dose 25 mg), adjusted according to response to 50 mg daily, lower initial dose may be used in intravascular volume depletion, maximum 50 mg per day

Child 6–17 years (under expert supervision) (body weight 50 kg and above): Initially 50 mg once daily, adjusted according to response to 1.4 mg/kg once daily, maximum 100 mg per day

Hypertension with intravascular volume depletion

Child 6–17 years (under expert supervision) (body weight 50 kg and above): Initially 25 mg once daily, adjusted according to response to 1.4 mg/kg once daily, maximum 100 mg per day

Contraindications: Hypersensitivity to the active substance or to any of the excipients, 2nd and 3rd trimester of pregnancy, Severe hepatic impairment, electrolyte imbalance

Precautions: Severe heart failure, aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Hepatic Impairment: Contraindicated in severe impairment. Consider dose reduction if history of mild or moderate impairment (risk of increased plasma concentrations). Not recommended for children with hepatic impairment.

Renal Impairment: Monitor renal function during treatment. No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients. Not recommended for children with eGFR < 30 mL/min/1.73 m2

Pregnancy: The use of Losartan is not recommended during the first trimester of pregnancy. The use of Losartan is contraindicated during the 2nd and 3rd trimester of pregnancy.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Hypoglycaemia, dizziness, vertigo, hyperkalaemia, hypotension, dyspnoea, cough, liver disorder, hypersensitivity, depression, malaise, urinary tract infection, renal impairment.

Interactions with other medicines (*indicates serious):

ACEI, drugs that cause hypotension (e.g., tricyclic antidepressants, antipsychotics), *lithium, NSAIMs, medicinal products which cause potassium retention (e.g. spironolactone, amiloride).

Telmisartan

ATC code: C09CA07

Tablet, 40 mg, 80 mg, LOU 4

Indications and dose

Adult

Hypertension, oral: Initially 20–40 mg once daily for at least 4 weeks, increased if necessary up to 80 mg once daily

Prevention of cardiovascular events in patients with established atherosclerotic cardiovascular disease or type 2 diabetes mellitus with target-organ damage, oral: 80 mg once daily

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Hypersensitivity to the active substance or to any of the excipients, Second and third trimester of pregnancy, Biliary obstructive disorders, Cholestasis, Severe hepatic impairment.

Precautions: Electrolyte imbalance, Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy.

Hepatic Impairment: Contraindicated in severe hepatic impairment. In patients with mild to moderate hepatic impairment, the dose should not exceed 40 mg once daily

Renal Impairment: Limited experience available in patients with severe renal impairment or haemodialysis. A lower starting dose of 20 mg is recommended in these patients. Monitor potassium and creatinine serum levels.

Pregnancy: Treatment with Angiotensin II receptor antagonist should be stopped immediately pregnancy is noted and if appropriate alternative therapy should be started.

Breastfeeding; Not recommended

Adverse effects: See Losartan Adverse effects

Interactions: See Losartan interactions.

14.3.3. Beta Blockers (BBs)

Bisoprolol

See Bisoprolol in section 14.1 Antianginal medicines

Labetalol

ATC code: C07AG01

Injection, 5 mg/mL (20-mL amp), LOU 4

Tablet, 100mg, 200mg, LOU 3

Indications and dose

Adult

Hypertensive emergencies, by IV injection: 50 mg, dose to be given over at least 1 minute, then 50 mg after 5 minutes if required, maximum 200 mg per course.

By IV infusion: Initially 2 mg/min until a satisfactory response is achieved, then discontinue; usual dose 50–200 mg.

Hypertension following MI, by IV infusion: 15 mg/hour, then increased to up to 120 mg/hour, dose to be increased gradually.

Hypertension of pregnancy, oral: Initially 100 mg twice daily, dose to be increased at intervals of 14 days; usual dose 200 mg twice daily, increased if necessary up to 800 mg daily in 2 divided doses, to be taken with food, higher doses to be given in 3–4 divided doses; maximum 2.4 g per day.

By IV infusion: Initially 20 mg/hour, then increased if necessary to 40 mg/hour after 30 minutes, then increased if necessary to 80 mg/hour after 30 minutes, then increased if necessary to 160 mg/hour after 30 minutes, adjusted according to response; usual maximum 160 mg/hour.

Paediatric: The safety and efficacy of labetalol in children has not been established. Unlicensed use for hypertensive emergencies must be prescribed under specialist advise.

Contraindication: Cardiogenic shock, Uncontrolled, incipient or digitalis refractory heart failure, Sick sinus syndrome (including sino-atrial block), Second or third degree heart block, Prinzmetal's angina, History of wheezing or asthma, Untreated phaeochromocytoma, Metabolic acidosis, Bradycardia (<45–50 bpm), Hypotension, Hypersensitivity to labetalol, Severe peripheral circulatory disturbances, Where peripheral vasoconstriction suggests low cardiac output, the use of Labetalol Injection to control hypertensive episodes following acute MI is contraindicated.

Precautions: Peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), pulse rate of 50 – 55 bpm, first degree heart block, psoriasis.

Hepatic Impairment: Avoid in liver damage, severe hepatocellular injury reported. Monitor liver function and consider dose reduction.

Renal Impairment: Dose reduction may be required

Pregnancy: not known to be harmful, except possibly in the first trimester. If labetalol is used close to delivery, infants should be monitored for signs of alpha-blockade (as well as beta blockade).

Breastfeeding: Infants should be monitored as there is a risk of possible toxicity due to alpha-blockade (in addition to beta-blockade).

Adverse effects: Drug fever, hypersensitivity, urinary disorders, Hepatic disorders, SLE, toxic myopathy, tremor, Cyanosis, hyperkalaemia, interstitial lung, lichenoid keratosis, muscle cramps, nasal congestion, peripheral oedema, photosensitivity reaction, postural hypotension, psychosis

Interactions: See Carvedilol interaction in section 14.1 Antianginal Medicines.

Metoprolol

ATC code: C07AB

Tablet (e/r), 25mg, 50mg, LoU 3

Indications and dose

Adult

Hypertension Initially 100 mg daily, increased if necessary to 200 mg daily in 1–2 divided doses, high doses are rarely required.

Arrhythmias: Usual dose 50 mg 2–3 times a day, then increased if necessary up to 300 mg daily in divided doses.

Paediatric

Not recommended in children

Contraindications: Hypersensitivity to the active substancesSevere peripheral arterial disease, untreated pheochromocytoma, metabolic acidosis, severe asthma or history of severe bronchospasm. Cardiovascular system (Atrioventricular block of second or third degree, uncontrolled heart failure, clinically relevant sinus bradycardia, sick-sinus syndrome, Cardiogenic shock, Hypotension)

Precautions: Beta- blockers should be avoided in patients with reversible obstructive airway disease. Beta-blockers should be given with caution to patients with first degree atrioventricular block. Metoprolol may aggravate bradycardia and symptoms of peripheral arterial circulatory disorders.

Anaphylactic reaction: Whenever possible, beta-blockers, including metoprolol, should be avoided for patients who are at increased risk of anaphylaxis.

Abrupt cessation of therapy with a beta-blocker should be avoided, especially in patients with ischaemic heart disease. When possible, metoprolol should be withdrawn gradually over a period of 10 days, the doses diminishing to 25 mg for the last 6 days.

Hepatic impairment: Low dosage should be considered in severe hepatic dysfunction.

Renal impairment: No dose adjustment is needed.

Pregnancy: Metoprolol should not be used in pregnancy unless it is considered that the benefit outweighs the possible risk to the foetus/infant

Breastfeeding: Not recommended

Adverse effects: Constipation, palpitations, postural disorders, chest pain, drowsiness, dystrophic skin lesion, muscle cramps, oedema, skin reactions, weight

increased, hyperhidrosis .

Interactions with other medicines (*indicates serious):

Risk of hypotension when metoprolol is co administered with clonidine, prazosin or nitroglycerin.

Cardiac toxicity: (verapamil and diltiazem) risk of cardiac arrest. Digitalis glycosides may result in excessive bradycardia and/or increase in atrioventricular conduction time. Non-steroidal anti-inflammatory drugs: Indomethacin may decrease the antihypertensive effect of metoprolol.

In a patient under beta-blockade, the anaesthetic selected should be one exhibiting as little negative inotropic activity as possible (halothane/nitrous oxide). The patient may be protected against vagal reactions by intravenous administration of atropine.

Lignocaine: Metoprolol may impair the elimination of lignocaine

Notes:

» Metoprolol therapy should be brought to the attention of the anaesthetist prior to general anaesthesia. The benefits of continuing a treatment with a beta-blocker, including metoprolol, should be balanced against the risk of withdrawing it in each patient. When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation. However, the risk of hypertension may be increased. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs.

Nebivolol

ATC code: C07AB12

Tablet, 2.5 mg, 5 mg LOU 3

Indications and dose

Adult

Essential hypertension: 5 mg daily may be increased every 2 weeks; not to exceed 40 mg/day.

Elderly: Initially 2.5 mg once daily, then increased if necessary to 5 mg once daily

Hypertension in patient with renal impairment: Initially 2.5 mg once daily, then increased if necessary to 5 mg once daily.

Paediatric

Not recommended

Contraindications:

Acute or decompensated heart failure requiring intravenous inotropes.

Hepatic impairment: Avoid.

Renal impairment:

CrCl >30-80 mL/min: Dose adjustment not listed by the manufacturer.

CrCl <30 mL/min: 2.5 mg/day PO initially; increased cautiously.

Pregnancy: Not recommended

Breastfeeding: Avoid

Adverse effects: Constipation, oedema, postural hypertension

Interactions with other medicines (*indicates serious): Beta blockers, selective: increase the risk of hypertension and bradycardia when given with sympathomimetics, vasoconstrictor (*adrenaline/epinephrine, noradrenaline/norepinephrine).

Fedratinib is predicted to increase the exposure to nebivolol.

Givosiran is predicted to increase the exposure to nebivolol.

*Calcium channel blockers (verapamil) increase the risk of cardiovascular adverse effects

Cinacalcet and Dacomitinib is predicted to increase the exposure to selective beta blockers

14.3.4. Calcium Channel Blockers (CCBs)

Amlodipine

ATC code: C08CA01

Tablet, 5 mg, 10 mg, LOU 3

Indications and dose

Adult

Angina, oral: Initially 5 mg once daily, increased if necessary; maximum 10 mg once daily

Hypertension, oral: Initially 5 mg once daily, increased if necessary; maximum 10 mg once daily

Paediatric

Hypertension, oral

Child 1 month–11 years: Initially 100–200 micrograms/kg once daily, increased if necessary up to 400 micrograms/kg once daily, adjusted at intervals of 1–2 weeks; maximum 10 mg per day

Child 12 years and over: Give adult dose

Contraindications: severe hypotension, hypersensitivity to amlodipine, cardiogenic shock, unstable angina, significant aortic stenosis, haemodynamically unstable heart failure after acute MI (during the first 28 days)

Precautions: congestive heart failure, elderly

Hepatic impairment: May need dose reduction, consider initial dose of 2.5 mg due to prolonged half-life.

Renal Impairment: No dose change needed.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: palpitation, flushing, oedema, headache, dizziness, sleep disturbances, fatigue, GI disturbances, constipation, dry mouth, hypotension, syncope, chest pain, dyspnoea, rhinitis, mood changes, tremor, paraesthesia, increased sweating, urinary disturbances, impotence, gynaecomastia, myalgia,

arthralgia, muscle cramps, visual disturbances, tinnitus, pruritus, rash (including isolated reports of erythema multiforme), purpura, and skin discoloration, gastritis, pancreatitis, hepatitis, jaundice, cholestasis, gingival hyperplasia, MI, arrhythmias, vasculitis, coughing, hyperglycaemia, thrombocytopenia, peripheral neuropathy, angioedema, and urticaria.

Interactions with other medicines (*indicates serious): *phenobarbitone, *ritonavir, acetazolamide, alcohol, amiloride, atenolol, chlorpromazine, furosemide, glyceryl trinitrate, ibuprofen, enalapril, hydralazine, spironolactone, ketamine, carbamazepine, phenytoin, oestrogens, CYP3A4 inhibitors (e.g., Clarithromycin, erythromycin), CYP3A4 inducers e.g., rifampin, IV magnesium.

Nifedipine

ATC code: C08CA05

Tablet (slow release), 20 mg, LOU 3

Indications and dose

Hypertension, angina prophylaxis, oral: 10 mg twice daily, adjusted according to response to 40 mg twice daily

Paediatric: No or insufficient experience with slow-release tablets in children and adolescents, therefore its use is not recommended.

Contraindications: Acute attacks of angina, cardiogenic shock, significant aortic stenosis, unstable angina, within 1 month of MI

Precautions: Diabetes mellitus, elderly, heart failure, ischaemic pain, poor cardiac reserve, severe hypotension, short-acting formulations are not recommended for angina or long-term management of hypertension (their use may be associated with large variations in blood pressure and reflex tachycardia), significantly impaired left ventricular function (heart failure deterioration observed)

Hepatic impairment: Mild, moderate or severe liver dysfunction, monitor carefully and a dose reduction may be necessary.

Renal Impairment: no dosage adjustment is required

Pregnancy: May inhibit labour, avoid before week 20, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension. Use only if other treatment options are not indicated or have failed.

Breastfeeding: Nifedipine is excreted in the breast milk. No or insufficient data on the effect on the infant therefore its use is not recommended.

Adverse effects: Constipation, malaise, oedema, vasodilation, Allergic oedema, anxiety, chills, diarrhoea, dry mouth, epistaxis, GI disorders, hypotension, joint disorders, laryngeal oedema, migraine, pain, sleep disorders, tremor, urinary disorders, vertigo, vision disorders, mood altered, Agranulocytosis, bezoar, cerebral ischaemia, chest pain, dysphagia, dyspnoea, eye pain, gingival disorder, gynaecomastia (following long term use), hepatic disorders, hyperglycaemia, ischaemic heart disease, leucopenia, myasthenia gravis aggravated, photoallergic reaction, pulmonary oedema, telangiectasia, toxic epidermal necrolysis.

Interactions with other medicines (*indicates serious): * Digoxin, Grapefruit juice, *Magnesium (parenteral), *Propranolol, *Rifampicin, *phenytoin, *phenobarbital, *atenolol, alcohol, carbamazepine, ciclosporin, enalapril, haloperidol, hydrocortisone, ibuprofen, insulins, furosemide, glyceryl trinitrate, hydralazine, halothane, ketamine, oestrogens, diazepam, chlorpromazione.

14.3.5. Thiazide and Thiazide-Like Diuretics

Chlorthalidone

ATC code: C03BA04

Tablet, 12.5 mg, LOU 4

Indications and dose

Adults

Hypertension: 25 mg daily, dose to be taken in the morning, then increased if necessary to 50 mg daily

Paediatric: Not recommended

Contraindications: Patients presenting with anuria. Hypersensitivity to chlorthalidone or sulfonamides

Precautions: Use with caution in diabetes mellitus, fluid or electrolyte imbalance, advanced age, history of allergy or bronchial asthma, patients with hyperuricemia or gout, hypercholesterolemia, hypotension, systemic lupus erythematosus, liver disease, severe renal disease

Hepatic impairment: Not recommended.

Renal impairment:

CrCl <10 mL/min: Ineffective; do not use.

CrCl >10 mL/min: Dose adjustment not necessary

Pregnancy: Not recommended

Breastfeeding: should be avoided. Large doses may suppress lactation.

Adverse effects: Eosinophilia, glycosuria, hepatic disorders, hypotension, anorexia, dyslipidemia, hypokalemia gastrointestinal discomfort, arrhythmia, diabetes mellitus exacerbated, risk of male sexual dysfunction, photosensitization may occur.

Interactions with other medicines (*indicates serious):

Hypersensitivity with allopurinol, risk of acute renal failure with aspirin. Thiazide diuretics are predicted to increase the risk of

hypercalcaemia when given with toremifene and vitamin D substances. Avoid concurrent use with lithium (reduction of lithium dosage by 50% may be necessary).May aggravate digitalis toxicity

Notes:

» Can be used in mild to moderate chronic heart failure: Adult: 25–50 mg daily, dose to be taken in the morning, then increased if necessary to 100–200 mg daily, reduce to lowest effective dose for maintenance.

Hydrochlorothiazide (HCTZ)

ATC code: C03AA03

Tablet (scored), 25 mg, LOU 3

Indications and dose

Adult

Heart failure, oral: Initially 25 mg daily on rising, increased to 50 mg daily, if necessary

» **Elderly**: Initially 12.5 mg daily on rising

Hypertension, oral: 12.5 mg daily, increased to 25–50 mg daily if necessary.

Oedema, oral: Initially 25 mg daily on rising, increased to 50 mg daily if necessary

» **Elderly**: Initially 12.5 mg daily on rising

Severe oedema in patients unable to tolerate loop diuretics, oral: Up to 100 mg either daily or on alternate days (maximum, 100 mg daily)

Nephrogenic diabetes insipidus, oral: Initially up to 100 mg daily

Paediatric

Oedema, oral

Infant under 6 months: 2–3.3 mg/kg daily in two divided doses; maximum dose 37.5 mg daily

Child over 6 months: 2 mg/kg daily in two divided doses; maximum dose 200 mg daily

Hypertension, oral,

Child all ages: Initially 1 mg/kg once daily; may increase to a maximum 3 mg/kg daily (maximum 50 mg daily)

Contraindications: Severe renal or severe hepatic impairment, hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia, Addison disease.

Precautions: the elderly, electrolytes may need to be monitored with high doses or in renal impairment, may aggravate diabetes mellitus and gout, may exacerbate SLE, porphyria.

Hepatic impairment, contraindicated in severe impairment, uptitrate with caution in moderate to severe impairment

Renal Impairment: contraindicated in severe impairment. Hydrochlorothiazide may be ineffective in moderate to severe impairment. Monitor electrolytes.

Pregnancy: Not used to treat hypertension in pregnancy third trimester: May cause neonatal thrombocytopenia

Breastfeeding: Continue breastfeeding, may inhibit breastfeeding

Adverse effects: fluid and electrolyte imbalance leading to dry mouth, thirst, GI disturbances (including nausea, and vomiting), weakness, lethargy, drowsiness, seizures, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, and arrhythmias, hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis, hypercalcaemia, hyperglycaemia, hyperuricaemia, gout, rash, photosensitivity, dyslipidaemia (increased total cholesterol, LDL and triglyceride concentrations and reduced HDL concentration), rarely impotence (reversible), blood disorders including neutropenia, and thrombocytopenia, pancreatitis, intrahepatic cholestasis, acute renal failure, hypersensitivity reactions including pneumonitis, pulmonary oedema, and severe skin reactions.

Interactions with other medicines (*indicates serious), Alcohol, Allopurinol, Amitriptyline, Amlodipine, Amphotericin B, Atenolol, Calcium, Carbamazepine, Chlorpromazine, Ciclosporin, Cisplatin, Clomipramine, Oestrogens, Dexamethasone, Diazepam, *Digoxin, *Enalapril, Ergocalciferol, Fluconazole, Fluphenazine, Furosemide, Glibenclamide, Glyceryl trinitrate, Halothane, Hydralazine, Hydrocortisone, Ibuprofen, Insulins, Isosorbide dinitrate, Ketamine, Levodopa, *Lidocaine, *Lithium, Metformin, methyldopa, nifedipine, nitrous oxide, prednisolone, propranolol, *quinidine, salbutamol, sodium nitroprusside, thiopental, timolol, verapamil.

Indapamide

ATC code : C03BA11

Tablet, 1.5 mg LoU 4

Indications and dose

Adult

Essential hypertension: 1.5 mg daily, dose to be taken preferably in the morning, may increase at 4-week intervals up to 5 mg.

Paediatric: Not recommended

Contraindications: Acute porphyrias, hypersensitivity to indapamide or sulfonamides Anuria

Precautions: To be used in caution in patients presenting with hypercholesterolemia, hypotension, systemic lupus erythematosus, liver disease or severe renal disease, angle closure glaucoma fluid or electrolyte imbalance, advanced age, history of allergy or bronchial asthma, patients with hyperuricemia or gout,

Hepatic impairment: Should be used with caution. Fluid and electrolyte balance may precipitate hepatic coma.

Renal impairment: No renal dose adjustment required.

Pregnancy: May be used (category B).

Breastfeeding: Avoid

Adverse effects: Angioedema, arrhythmias, dry mouth, hemolytic anemia, hepatic disorders, renal failure.

Interactions with other medicines (*indicates serious): Risk of acute renal failure when given with NSAIDS. Reboxetine is predicted to increase the risk of hypokalaemia when given with thiazide diuretics. Thiazide diuretics are predicted to increase the risk of hypercalcaemia when given with toremifen vitamin D substances.

14.3.6. Other Anti-Hypertensive Agents

14.3.6.1. Centrally acting antihypertensive agents

Methyldopa

ATC code: C02AB02 (racemic)

Tablet (f/c), 250 mg, 500 mg, LOU 4

Indications and dose

Adult

Hypertension in pregnancy, oral: Initially 250 mg 2–3 times daily, gradually increased at intervals of 2 or more days, if necessary; maximum 3 g daily

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: depression, active liver disease, phaeochromocytoma, porphyria.

Precautions: blood counts and liver-function tests advised, history of depression, positive direct Coomb test in up to 20% of patients (affects blood cross-matching), interference with laboratory tests. May impair ability to perform skilled tasks, for example, operating machinery or driving.

Hepatic Impairment: Caution in history of liver disease, avoid in active liver disease

Renal Impairment: In moderate impairment**,** start with small dose, increased sensitivity to hypotensive and sedative effects

Pregnancy: Not known to be harmful

Breastfeeding: Amount too small to be harmful

Adverse effects: sedation, dizziness, lightheadedness, postural hypotension, weakness, fatigue, headache, fluid retention and oedema, sexual dysfunction, impaired concentration and memory, depression, mild psychosis, disturbed sleep and nightmares, drug fever, influenza-like syndrome, nausea, vomiting, constipation, diarrhoea, dry mouth, stomatitis, sialadenitis, liver function impairment, hepatitis, jaundice, rarely fatal hepatic necrosis, bone marrow depression, haemolytic anaemia, leukopenia, thrombocytopenia, eosinophilia, parkinsonism, rash including toxic epidermal necrolysis, nasal congestion, black or sore tongue, bradycardia, exacerbation of angina, myalgia, arthralgia, paraesthesia, Bell palsy, pancreatitis, hypersensitivity reactions including lupus erythematosus-like syndrome, myocarditis, pericarditis, gynaecomastia, hyperprolactinaemia, amenorrhoea, urine darkens on standing.

Interactions with other medicines: Lithium, Other antihypertensive medicines, sympathomimetics, phenothiazines, tricyclic antidepressants and MAOIs, Iron.

14.3.6.2. Potassium-Sparing Diuretics

Spironolactone

ATC code: C03DA01

Tablet (scored), 25 mg, LOU 4

Indications and dose

Refractory oedema in congestive heart failure, adjunct to ACEI and a loop or thiazide diuretic in severe congestive heart failure, nephrotic syndrome, hepatic cirrhosis with ascites and oedema, ascites associated with malignancy, primary hyperaldosteronism

Adult

Oedema, oral: 100–200 mg daily, increase if necessary to 400 mg daily in resistant oedema; usual maintenance dose, 25–200 mg daily

Primary hyperaldosteronism, oral: 400 mg daily for 3–4 weeks

Preoperative management, oral: 100–400 mg daily, if not suitable for surgery, give the lowest effective dose for long-term maintenance

Adjunct in severe heart failure, oral: usually 25 mg daily

Paediatric

Oedema, oral

Initially 1–3 mg/kg daily in 1–2 divided doses

Contraindications: hyperkalaemia, hyponatraemia, moderate renal impairment,

Addison disease.

Precautions: monitor blood urea nitrogen and plasma electrolytes (discontinue

if hyperkalaemia), the elderly (reduce dose), diabetes mellitus, porphyria, monitor high doses (carcinogenic in rodents).

Hepatic Impairment: Caution is required in patients with hepatic disorders due to the risk of hepatic coma

Renal Impairment, Avoid in acute renal insufficiency or severe impairment. Monitoring Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).

Pregnancy: Use only if potential benefit outweighs risk— feminisation of male fetus in animal studies.

Breastfeeding: Metabolites present in milk but amount probably too small to be harmful.

Adverse Effects: Hyperkalaemia, hyponatraemia, hyperchloraemic acidosis, dehydration (for symptoms of fluid and electrolyte imbalance, transient increase in blood urea nitrogen, diarrhoea, gynaecomastia, menstrual irregularities, impotence, hirsutism, deepening of voice, rash, ataxia, fever, hepatotoxicity.

Interactions with other medicines (*indicates serious): Acetylsalicylic acid, Alcohol, Amitriptyline, Amlodipine, Atenolol, Carbamazepine, Chlorpromazine, * Ciclosporin, Cisplatin, Clomipramine, Oestrogens, Dexamethasone, Diazepam, *Digoxin, *Enalapril, Fluphenazine, Glyceryl trinitrate, Halothane, Hydralazine, Hydrocortisone, Ibuprofen, Isosorbide dinitrate, Ketamine, Levodopa, *Lithium, Methyldopa, Nifedipine, Nitrous oxide, * potassium salts, prednisolone, propranolol, sodium nitroprusside, Thiopental, Timolol, Verapamil.

14.3.6.3. Vasodilators

Hydralazine

ATC code: C02DB02

Tablet (scored), 25 mg (as HCl), LOU 3

Tablet (scored), 50 mg (as HCl), LOU 3

Injection, 20 mg (as HCl), LOU 4

Indications and dose

In combination therapy in moderate to severe hypertension, hypertensive crises, hypertension associated with pregnancy (including pre-eclampsia or eclampsia), heart failure

Adult

Moderate to severe hypertension (adjunct), oral: Initially 25 mg twice daily, increase if necessary up to 50 mg twice daily

Heart failure (with long-acting nitrate) (initiated in hospital or under specialist supervision), oral: Initially 25 mg 3–4 times a day, subsequent doses to be increased every 2 days if necessary; usual maintenance 50–75 mg 4 times a day

Hypertensive emergencies (including during pregnancy), hypertension with renal complications, by IV infusion: Initially 200–300 micrograms/min, usual maintenance 50–150 micrograms/min.

Hypertensive emergencies (including during pregnancy), hypertension with renal complications, by slow iv injection: 5–10 mg, to be diluted with 10 mL sodium chloride 0.9%, dose may be repeated after 20–30 minutes

Paediatric

Resistant hypertension (adjunct), oral

Neonate: 250 to 500 micrograms/kg every 8 to 12 hours, increase if necessary to a maximum of 2 to 3 mg/kg every 8 hours

Child 1 month–11 years: 7.5 mg/kg (maximum 200 mg) daily

Child 12 years and over: Use adult dose

Resistant hypertension (adjunct), slow IV injection

Neonate to child 11 years: 100 to 500 micrograms/kg, repeated every 4 to 6 hours as necessary (maximum 3 mg/kg or 60 mg daily)

Child 12 years and over: 5 to 10 mg, repeated every 4 to 6 hours as necessary

Resistant hypertension (adjunct), continuous IV infusion (preferred route in cardiac patients)

Neonate: 12.5 to 50 micrograms/kg per hour, to a maximum of 2 mg/kg daily

Neonate 1 month and over and child 1 to 11 years: 3 mg/kg daily

Child 12 years and over: 3 to 9 mg/hour (maximum 3 mg/kg daily)

Contraindications: idiopathic SLE, severe tachycardia, high output heart failure, myocardial insufficiency due to mechanical obstruction, cor pulmonale, dissecting aortic aneurysm, porphyria

Precautions: coronary artery disease (may provoke angina, avoid after MI until stabilized), cerebrovascular disease, occasionally over-rapid blood pressure reduction even with low parenteral doses.

Hepatic Impairment: Reduce dose (risk of accumulation).

Renal Impairment: In mild impairment, reduce dose if CrCl less than 30 mL/min

Pregnancy: Neonatal thrombocytopenia reported, but risk should be balanced against risk of uncontrolled maternal hypertension. Avoid during first and second trimesters, no reports of serious harm following use in third trimester.

Breastfeeding: Present in milk but not known to be harmful, monitor infant

Adverse effects: tachycardia, palpitations, postural hypotension, fluid retention, GI disturbances including anorexia, nausea, vomiting, diarrhoea, and rarely constipation, dizziness, flushing, headache, abnormal liver function, jaundice, SLE-like syndrome, particularly in women and slow acetylators, nasal congestion, agitation, anxiety, polyneuritis, peripheral neuritis, rash, fever, paraesthesia, arthralgia, myalgia, increased lacrimation, dyspnoea, raised plasma creatinine, proteinuria, haematuria, blood disorders including haemolytic anaemia, leukopenia, and thrombocytopenia.

Interactions: Acetazolamide, Alcohol, Amiloride, Amlodipine, Atenolol, Chlorpromazine, Oestrogens, Dexamethasone, Diazepam, Enalapril, Fluphenazine, Furosemide, Glyceryl trinitrate, Halothane, Hydrochlorothiazide, Ibuprofen, Isosorbide dinitrate, Ketamine, levodopa, methyldopa, nifedipine, nitrous oxide, prednisolone, propranolol, sodium nitroprusside, spironolactone, thiopental, timolol, verapamil.

14.3.6.4. Alpha 1 Receptor Blockers

Doxazosin

ATC code: C02CA04

Tablet, 2 mg, LOU 4

Indications and dose

Adult

Hypertension, oral: Initially 1 mg once daily for 1–2 weeks, then increased to 2 mg once daily, then increased if necessary to 4 mg once daily; maximum 16 mg per day

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Hypersensitivity to the active substance or other types of quinazolines (e.g., prazosin, terazosin, doxazosin) or to any of the excipients, History of micturition syncope (in patients with benign prostatic hypertrophy), history of postural hypotension, monotherapy in patients with overflow bladder or anuria.

Precautions: Care with initial dose (postural hypotension), cataract surgery (risk of intra-operative floppy iris syndrome), elderly, heart failure, pulmonary oedema due to aortic or mitral stenosis.

Hepatic Impairment: Limited data, use with caution in mild to moderate impairment, avoid in severe impairment.

Renal Impairment: Since there is no change in pharmacokinetics in patients with impaired renal function, the usual adult dose of doxazosin is recommended.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: Accumulates in milk in animal studies. No or insufficient data on the amount of drug excreted

in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Arrhythmias, asthenia, chest, pain, cough, cystitis, dizziness, drowsiness, dry mouth, somnolence, headache, vertigo, palpitation, tachycardia, hypotension especially with first dose, bronchitis, rhinitis, GI disturbance, dyspnoea, increased risk of infection, influenza like illness, muscle complaints, oedema, pain, palpitations, skin reactions, urinary disorders.

Interactions: Phosphodiesterase-5-inhibitors (e.g., Sildenafil, tadalafil), strong CYP 3A4 inhibitor, such as clarithromycin, itraconazole, ketoconazole, ritonavir or voriconazole, other antihypertensives.

Prazosin

ATC code: C02CA01

Capsule, 500 micrograms, 1 mg, 5 mg, LOU 4

Indications and dose

Adult

Hypertension, oral: Initially 500 micrograms 2–3 times a day for 3–7 days; initial dose should be taken on retiring to bed at night to avoid collapse, increased to 1 mg 2–3 times a day for a further 3–7 days, then increased if necessary up to 20 mg daily in divided doses

Congestive heart failure (rarely used), oral: 500 micrograms 2–4 times a day, initial dose to be taken at bedtime, then increased to 4 mg daily in divided doses; maintenance 4–20 mg daily in divided doses

Benign prostatic hyperplasia, oral: Initially 500 micrograms twice daily for 3–7 days; subsequent doses should be adjusted according to response; maintenance 2 mg twice daily

» **Elderly**: Initiate with lowest possible dose

Paediatric

Hypertension, oral

Child 1 month–11 years: Initially 10–15 micrograms/kg 2–4 times a day, initial dose to be taken at bedtime, then increased to 500 micrograms/kg daily in divided doses, dose to be increased gradually, maximum 20 mg per day

Child 12–17 years: Initially 500 micrograms 2–3 times a day for 3–7 days, initial dose to be taken at bedtime, then increased to 1 mg 2–3 times a day for a further 3–7 days, then increased if necessary up to 20 mg daily in divided doses, dose should be increased gradually

Congestive heart failure (rarely used), oral

Child 1 month–11 years: 5 micrograms/kg twice daily, initial dose to be taken at bedtime, then increased to 100 micrograms/kg daily in divided doses, doses should be increased gradually.

Contraindications: History of micturition syncope (in patients with benign prostatic hyperplasia), history of postural hypotension, not recommended for congestive

heart failure due to mechanical obstruction (e.g., aortic stenosis).

Precautions: Cataract surgery (risk of intra-operative floppy iris syndrome), elderly, first dose hypotension

Hepatic Impairment: Initial dose reduction to 500 micrograms daily, increased with caution

Renal Impairment: Initially 500 micrograms daily in moderate to severe impairment, increased with caution.

Pregnancy: No evidence of teratogenicity, insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: Use with caution. Present in milk, amount probably too small to be harmful.

Adverse effects: Asthenia, constipation, depression, diarrhoea, dizziness, drowsiness, dry mouth, dyspnoea, headache, nasal congestion, nausea, nervousness, oedema, palpitations, postural hypotension, sexual dysfunction, skin reactions, syncope, urinary

Disorders, vertigo, vision blurred, vomiting, hepatic dysfunction, pancreatitis.

Interactions: Phosphodiesterase 5 inhibitors (e.g., sildenafil, tadalafil), betablockers, CCBs.

Notes:

First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patients should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely.

14.3.6.5. Non Selective Alpha 1 Adrenoceptor Antagonist

Phenoxybenzamine

ATC code: C04AX02

Capsule, 10 mg, LOU 5

Indications and dose

Adult

Hypertension in phaeochromocytoma, oral: Initially 10 mg daily, increased in steps of 10 mg daily until hypeooortension controlled or treatment not tolerated, maintenance 1–2 mg/kg daily in 2 divided doses

» **Elderly**: 10 mg dose should be sufficient

Paediatric

Hypertension in phaeochromocytoma, oral

Child: 0.5–1 mg/kg twice daily, adjusted according to response

Contraindications: During recovery period after MI (usually 3–4 weeks), history of cerebrovascular accident

Precautions: Avoid in Acute porphyrias, carcinogenic in animals, cerebrovascular disease,

congestive heart failure, elderly, severe ischaemic heart disease.

Hepatic impairment: No or insufficient data on the pharmacokinetics of this drug in hepatic impairment. Therefore, uptitration should be done with caution.

Renal impairment: Use with caution.

Pregnancy: Hypotension may occur in newborn.

Breastfeeding: May be present in milk.

Adverse effects: Abdominal distress, dizziness, ejaculation failure, fatigue, miosis, nasal congestion, postural hypotension, reflex tachycardia.

Notes:

» Handling and storage: Owing to risk of contact sensitisation health care professionals should avoid contamination of hands.

14.3.6.6. Others

Bosentan

ATC code: C02KX01

Tablet, (film coated) 62.5mg LOU 4

Indications and dose

Adult

Pulmonary arterial hypertension (initiated under specialist supervision)

> 40kg: Start 62.5 mg twice daily for 4 weeks, then increased to 125 mg twice daily (max. per dose 250 mg); maximum 500 mg per day.

<40 kg: Maintain dose at 62.5 mg twice daily.

Discontinuation of treatment: Consider a reduction in dosage to 62.5 mg twice daily for 3-7 days.

Paediatric

From 12 years of age and weighs less than 40Kg: 62.5 mg two times a day.

Below 12 years of age: Dose is based on body weight and must be determined by a specialist.

Contraindications: Pregnancy, hypersensitivity, concomitant cyclosporine or glyburide use,

Precautions: Dose-related decrease in hemoglobin and hematocrit may occur with treatment; it is recommended that hemoglobin concentrations be checked regularly.

Pulmonary edema may occur. Decreased sperm counts have been observed.

Hepatic impairment: Mild liver dysfunction: No adjustment recommended.

Elevated AST/ALT than 3 times the upper limit of normal: Use should be avoided.

Renal impairment: No adjustment recommended.

Pregnancy: Should be avoided

Breastfeeding: Not to be used

Adverse effects: headache, nasal congestion, palpitations, skin reactions, syncope anaemia, diarrhea, flushing, gastroesophageal reflux disease.

Interactions with other medicines (*indicates serious): Bosentan is metabolized by CYP2C9 and CYP3A. CYP2C9 (fluconazole, amiodarone) and CYP3A (ketoconazole, itraconazole, amprenavir, erythromycin, fluconazole, diltiazem) inhibitors may increase the plasma concentration of bosentan. Coadministration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A inhibitor with bosentan is not recommended.

Bosentan is an inducer of CYP3A and CYP2C9; plasma concentrations of drugs metabolized by these two isozymes will be decreased when co-administered with bosentan.

Reduces efficacy of hormonal contraceptive.

Sildenafil

ATC code: G04BE03

Tablet, 25 mg, LOU 4

Indications and dose

Adult

Pulmonary arterial hypertension, oral: 20 mg 3 times a day

Paediatric

Pulmonary artery hypertension, oral

Neonate: Initially 250–500 micrograms/kg every 4–8 hours, adjusted according to response; start with the lower dose and frequency, especially if used with other vasodilators; maximum 30 mg per day

Child 1–11 months: Initially 250–500 micrograms/kg every 4–8 hours, adjusted according to response; start with the lower dose and frequency, especially if used with other vasodilators; maximum 30 mg per day

Child 1–17 years (body weight up to 20 kg): 10 mg 3 times a day

Child 1–17 years (body weight 20 kg and above): 20 mg 3 times a day

Contraindications: Hereditary degenerative retinal disorder. History of non-arteritic anterior ischaemic optic neuropathy, recent history of MI, recent history of stroke, sickle-cell anaemia

Precautions: Active peptic ulceration, anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, Peyronie's disease). Autonomic dysfunction, bleeding disorders, cardiovascular disease, hypotension (avoid if severe). Intravascular volume depletion. Left ventricular outflow obstruction, predisposition to priapism (e.g., in sickle-cell disease, multiple myeloma, or leukaemia). Pulmonary veno-occlusive disease. Avoid abrupt withdrawal.

Pregnancy: Use only if potential benefit outweighs risk— no evidence of harm in animal studies.

Breastfeeding: avoid—no information available.

Hepatic Impairment: caution in mild to moderate impairment; avoid in severe impairment (no information available). Dose adjustments -if not tolerated, consider dose reduction in mild to moderate impairment— consult product literature.

Renal Impairment: Dose adjustments- Reduce dose if not tolerated

Adverse effects: Alopecia, anaemia, anxiety, cough, diarrhea, dizziness, fluid retention, GI discomfort, GI disorders, headaches. Increased risk of infection, insomnia, nasal Complaints, nausea, night sweats, pain, skin reactions, tremor, vasodilation, vision disorders, Arrhythmias, chest pain, drowsiness, dry eye, dry mouth, eye discomfort, eye disorders, eye inflammation, fatigue, feeling hot, gynaecomastia,

haemorrhage, hypertension, hypotension, myalgia, numbness, palpitations, sinus congestion, tinnitus, vertigo, vomiting, Acute coronary syndrome, arteriosclerotic retinopathy, cerebrovascular insufficiency, glaucoma, haematospermia, hearing impairment, irritability, optic neuropathy (discontinue if sudden visual impairment occurs), oral hypoaesthesia, priapism, retinal occlusion, scleral discolouration, seizure, SCARs, sudden cardiac death, syncope, throat tightness

Interactions with other medicines (*indicates serious): * nitrates such as isosorbide mononitrate or dinitrate, *nitroglyglycerin, Nelfinavir, ritonavir, saquinavir, *elvitegravir/cobicistat/emtricitabine/tenofovir, *alpha blockers (alfuzosin, doxazonie, prazosin), *CYP3A4 inhibitors (Conivaptan, crizotinib, dabrafenib, ketoconazole).

Tadalafil

ATC code: G04BE08

Tablet, 20mg, LOU 4

Indications and dose

Adult

Pulmonary arterial hypertension (initiated under specialist supervision) : 40 mg once daily

Paediatric

Safety and efficacy not established.

Contraindications: Mild to severe heart failure, patients in whom vasodilation or sexual activity are inadvisable, uncontrolled hypertension, unstable angina, stroke, arrhythmias, aortic and mitral valve disease, left ventricular dysfunction, life-threatening arrhythmias, pericardial congestive cardiomyopathy, coronary artery disease.

Precautions: Tadalafil has vasodilatory properties that may result in transient decreases in blood pressure. Patients with preexisting hypotension, with autonomic dysfunction, with left ventricular outflow obstruction, may be particularly sensitive to the actions of vasodilators.

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD).

Hepatic impairment: Mild-to-moderate (Child-Pugh class A or B): Consider starting dosage of 20 mg PO once daily Severe (Child-Pugh class C): Avoid use.

Renal impairment: Mild-to-moderate (CrCl 31-80 mL/min): 20 mg PO once daily initially; may be increased to 40 mg once daily on basis of tolerability Severe (CrCl <30 mL/min and on hemodialysis): Avoid use.

Pregnancy: Information not available

Breastfeeding: Not recommended

Adverse effects: Hypotension, headache, myalgia, nasal congestion, gastroesophageal reflux disease

Interactions with other medicines (*indicates serious): Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.

Co-administration of tadalafil tablet in Patients on Ritonavir: In patients receiving ritonavir for at least one week, start tadalafil tablet at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

Co-administration of Ritonavir in Patients on tadalafil tablet: Avoid use of tadalafil tablet during the initiation of ritonavir. Stop tadalafil tablet at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume tadalafil tablet at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

Potent Inhibitors of CYP3A: Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of tadalafil.

Potent Inducers of CYP3A: For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of tadalafil.

14.3.7. Combination Antihypertensive Medicines

FDC drugs are recommended because they minimize toxicity and therefore adverse effects as well as improve adherence to treatment.

Amlodipine + Hydrochlorthiazide (HCTZ)

ATC code: C08GA02

Tablet (FDC), Amlodipine 5 mg + hydrochlorothiazide 12.5 mg, LOU 3

Indications and use: Hypertension

See Amlodipine section 14.3.4 Calcium Channel Blockers

See Hydrochorothiazide section 14.3.5 Thiazide and Thiazide like diuretics

Dose, Contraindications, precautions, adverse effects, interactions with other medicines, notes:

See Amlodipine section 14.3.4 Calcium Channel Blockers

See Hydrochorothiazide section 14.3.5 Thiazide and Thiazide like diuretics

Amlodipine + Indapamide

ATC code: C08GA02

Tablet, 5 + 1.25mg, LOU 3

Indications and dose

Adult

Hypertension: To be used in patients who have stabilized BP and require multiple drugs or indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled on monotherapy.

For contraindications, dose adjustments, adverse effects and interactions – see individual monographs.

Lisinopril + Hydrochlorothiazide

ATC code: N/A

Tablet (FDC), Lisinopril 20 mg + hydrochlorothiazide 12.5 mg, LOU 3

Indications and use

Adult

Hypertension: 1 tablet once a day; in general, if the desired therapeutic effect cannot be achieved in 2 to 4 weeks at this dose level, the dose can be increased to two tablets administered once daily.

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Hypersensitivity to the active substances or to any of the excipients, Hypersensitivity to any other angiotensin-converting enzyme inhibitor (ACEI), Hypersensitivity to any sulphonamide-derived drugs, Concomitant use of Zestoretic with sacubitril/valsartan therapy. Zestoretic must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan, History of angioedema associated with previous ACEI therapy, Hereditary or idiopathic angioedema, Second and third trimesters of pregnancy, Severe renal impairment (CrCl < 30 mL/min), Anuria, Severe hepatic impairment.

Precautions:

See Hydrochlorthiazide section 14.3.5 Thiazide and Thiazide like diuretics.

See Enalapril section 14.3.1 Angiotensin Converting Enzyme Inhibitors

Volume-depletion, e.g., by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependant hypertension, Aortic and mitral valve stenosis/hypertrophic cardiomyopathy, ACEIs and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy, surgery.

Hepatic Impairment: Rarely, ACEIs have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. Patients receiving lisinopril/hydrochlorothiazide who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril/hydrochlorothiazide and receive appropriate medical follow-up.

Renal impairment: Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at CrCl values of 30 mL/min or below (i.e. moderate or severe renal insufficiency). This combination is not to be used as initial therapy in any patient with renal insufficiency. In patients with CrCl of >30 and <80 mL/min, combination may be used, but only after titration of the individual components. The recommended dose of lisinopril, when used alone, in mild renal insufficiency, is 5 to 10 mg.

Pregnancy: Use of ACEIs is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimester of pregnancy. Hydrochlorothiazide crosses the placenta. Hydrochlorothiazide's during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia. Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects, Interactions:

See Enalapril section 14.3.1 Angiotensin Converting Enzyme Inhibitors

See Hydrochlorthiazide section 14.3.5 Thiazide and Thiazide like diuretics

Note:

» Anaphylactoid reactions have been reported in patients, undergoing certain haemodialysis procedures (e.g., with the high-flux membranes AN 69 and during LDL apheresis with dextran sulphate) and treated concomitantly with an ACEI. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Losartan + Hydrochlorothiazide

ATC code: C09DA01

Tablet (FDC), Losartan 50 mg + hydrochlorothiazide 12.5 mg, LOU 3

Indications and use:

Hypertension: Losartan and hydrochlorothiazide is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the FDC may be considered in patients whose blood pressure is not adequately controlled.

Adult

Hypertension, oral: The usual maintenance dose of losartan + hydrochlothiazide is one tablet of 50 mg/12.5 mg (losartan 50 mg/HCTZ 12.5 mg) once daily.

For patients who do not respond adequately to 50 mg/12.5 mg, the dosage may be increased to two tablets (losartan 100 mg/HCTZ 25 mg) once daily.

The maximum daily dose is two tablets i.e., 100 mg/25 mg once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy.

Paediatric:

There is no experience in children and adolescents. Therefore, losartan/hydrochlorothiazide should not be administered to children and adolescents.

Dose, contraindications, precautions, adverse effects, interactions with other medicines, notes:

See Losartan section 14.3.2 Angiotensin receptor blocker

See Hydrochorothiazide section 14.3.5 Thiazide and Thiazide like diuretics

Renal impairment and haemodialysis: No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e., CrCl 30–50 mL/min). Losartan and hydrochlorothiazide tablets are not

recommended for haemodialysis patients. Losartan/hydrochlorothiazide (HCTZ) tablets must not be used in patients with severe renal impairment (i.e., CrCl <30 mL/min) (see section 4.3).

Use in patients with intravascular volume depletion: Volume and/or sodium depletion should be corrected prior to administration of losartan/HCTZ tablets.

Hepatic impairment: Losartan/HCTZ is contraindicated in patients with severe hepatic impairment.

Perindopril + Amlodipine

ATC code: C09BB04

Tablet, 5 mg + 5mg, 10 mg, LOU 3

Indications and dose

Adult

Hypertension: To be used in patients who have stabilized BP and require multiple drugs or indicated for the treatment of hypertension in patients whose blood pressure is not a dequately controlled on monotherapy.

For contraindications, dose adjustments, adverse effects and interactions – see individual monographs.

Perindopril + Amlodipine + Indapamide

ATC code: C09BX01

Tablet, 5 mg + 5 mg + 1.25 mg + 10 mg + 10 mg + 2.5 mg, LOU 4

Indications and dose

Adult

Hypertension: To be used in patients who have stabilized BP and require multiple drugs or

Indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled on monotherapy.

For contraindications, dose adjustments, adverse effects and interactions – see individual monographs.

Telmisartan + Amlodipine

ATC code: C09DB04

Tablet (FDC), telmisartan 40 mg + amlodipine 5 mg, LOU 3

Indications and use

Adult

Hypertension: Initiate with 40 mg/5 mg, may increase dose after at least 2 weeks, not to exceed 80 mg/10 mg per day; may be administered concomitantly with other antihypertensive agents

Contraindications, precautions, adverse effects, interactions with other medicines, notes:

See Telmisartan section 14.3.2 Angiotensin Receptor Blocker

See Amlodipine section 14.3.4 Calcium Channel Blockers

Telmisartan + Amlodipine + Hydrochlorothiazide

ATC code: C09DX08

Tablet, 40mg + 5mg + 12.5mg LOU 4

Indications and dose

Adult

Hypertension in patients stabilized on the individual components in the same proportions, or for hypertension not adequately controlled with telmisartan and amlodipine.

For contraindications, dose adjustments, adverse effects and interactions – see individual monographs.

Telmisartan + Hydrochlorothiazide

ATC code: C09DA07

Tablet (FDC), Telmisartan 40 mg + hydrochlorothiazide 12.5 mg LOU 3

Tablet (FDC), Telmisartan 80 mg + hydrochlorothiazide 12.5 mg LOU 3

Indications and use

Adult

Patients whose blood pressure is not adequately controlled by telmisartan alone should take telmisartan + hydrochlorthiazide. Individual dose titration with each of the two components is recommended before changing to the FDC. When clinically appropriate, direct change from monotherapy to the FDC may be considered.

Inadequately controlled blood pressure

- Telmisartan + hydrochlorthiazide 40 mg/12.5 mg once daily
- Telmisartan + hydrochlorthiazide 80 mg/12.5 mg once daily

Paediatric: The safety and efficacy of telmisartan + hydrochlorthiazide in children and adolescents has not been established. No data are available.

Contraindications, precautions, adverse effects, interactions with other medicines, notes:

See Telmisartan section 14.3.2 Angiotensin Receptor Blocker

See Hydrochlorthiazide section 14.3.5 Thiazide and Thiazide like diuretics

Renal impairment: Periodic monitoring of renal function is advised

Hepatic impairment: In patients with mild to moderate hepatic impairment the posology should not exceed telmisartan + hydrochlorthiazide once daily. Telmisartan + hydrochlorthiazide is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function.

14.4. Medicines Used In Heart Failure

Bisoprolol

See Bisoprolol in section 14.1 Antianginal medicines

Carvedilol

See Carvedilol in section 14.1 Antianginal medicines

Digoxin

See Digoxin in section 14.2 Antiarrhythmic medicines

Dobutamine

ATC code: C01CA07

Injection solution, 12.5 mg/mL, 20 mL, LOU 5

Indications and use

Adult

Inotropic support in infarction, cardiac surgery, cardiomyopathies, septic shock, cardiogenic shock, and during positive end expiratory pressure ventilation, by IV infusion: Usual dose 2.5–10 micrograms/kg/min, adjusted according to response, alternatively 0.5–40 micrograms/kg/min

Paediatric

Inotropic support in low cardiac output states, after cardiac surgery, cardiomyopathies, shock, by continuous IV infusion

Neonate: Initially 5 micrograms/kg/min, then adjusted according to response to 2–20 micrograms/kg/min; doses as low as 0.5–1 microgram/kg/min have been used

Child: Initially 5 micrograms/kg/min, then adjusted according to response to 2–20 micrograms/kg/min; doses as low as 0.5–1 microgram/kg/min have been used

Contraindications: Phaeochromocytoma, hypersensitivity to dobutamine or its excipients

Precautions: Acute heart failure, acute MI, arrhythmias, correct hypercapnia, hypovolaemia, hypoxia, metabolic acidosis before starting and during treatment. Diabetes mellitus, elderly, extravasation (may cause tissue necrosis), extreme caution or avoid in marked obstruction of cardiac ejection (such as idiopathic hypertrophic subaortic stenosis), hyperthyroidism, ischaemic heart disease, occlusive, vascular disease, severe hypotension, susceptibility to angle-closure glaucoma, tachycardia, tolerance may develop with continuous infusions longer than 72 hours.

Hepatic Impairment: No or insufficient data on the pharmacokinetics of this drug in renal/hepatic impairment. Therefore, uptitration should be done with caution.

Renal Impairment: No or insufficient data on the pharmacokinetics of this drug in renal/hepatic impairment. Therefore, uptitration should be done with caution.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Arrhythmias, bronchospasm, chest pain, dyspnoea, eosinophilia, fever, headache, inflammation localised, ischaemic heart disease, nausea, palpitations, platelet aggregation inhibition (on prolonged administration), skin reactions, urinary urgency, vasoconstriction, MI, Atrioventricular block, cardiac arrest, coronary vasospasm, hypertension or hypotension exacerbated, hypokalaemia.

Interactions: *betablockers (e.g., bisoprolol, propranolol), *linezolid.

Dopamine

ATC code: C01CA04

Injection, 40 mg/mL as HCl, 5mL vial, LOU 5

Indications and use

Cardiogenic shock including in MI and cardiac surgery

Adult

Cardiogenic shock, by infusion into a large vein: Initially 2–5 micrograms/kg/min, gradually increased by 5–10 micrograms/kg/min according to blood pressure, cardiac output, and urine output (seriously ill patients, up to 20–50 micrograms/kg/min)

Paediatric

Correct haemodynamic imbalance due to acute hypotension, shock, cardiac failure, adjunct following cardiac surgery, by continuous IV infusion

Neonate: Initially 3 micrograms/kg/min (max. per dose 20 micrograms/kg/min), adjusted according to response

Child: Initially 5 micrograms/kg/min (max. per dose 20 micrograms/kg/min), adjusted according to response

Contraindications: tachyarrhythmia, ventricular fibrillation, ischaemic heart

disease, phaeochromocytoma, hyperthyroidism, cyclopropane and halogenated hydrocarbon anaesthetics

Precautions: correct hypovolaemia before, and maintain blood volume during the treatment, correct hypoxia, hypercapnia, and metabolic acidosis before

or at same time as starting treatment, use low dose in cardiogenic shock due

to MI, history of peripheral vascular disease (increased risk of ischaemia of extremities), the elderly.

Hepatic impairment: No or insufficient data on the pharmacokinetics of this drug in hepatic impairment. Therefore, uptitration should be done with caution.

Renal impairment: No or insufficient data on the pharmacokinetics of this drug in renal impairment. Therefore, uptitration should be done with caution.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: nausea and vomiting, peripheral vasoconstriction, hypotension with dizziness, fainting, flushing, tachycardia, ectopic beats, palpitations, anginal pain, headache, dyspnoea, hypertension particularly in overdosage.

Interactions: Chlorpromazine, Ergometrine, Fluphenazine, Haloperidol, cyclopropane and halogenated hydrocarbon anaesthetics.

Empagliflozin

ATC code : A10BK03

Tablet, 10mg, LOU 5

Indications and dose

Adult

Symptomatic chronic heart failure with reduced ejection fraction (18–84 years): 10 mg once daily

Paediatric

Safety and efficacy not established for use in heart failure.

Contraindications: Diabetic ketoacidosis, serious hypersensitivity to empagliflozin

Precautions: Complicated urinary tract infections—discontinue treatment, for the elderly there's is risk hypotension and volume depletion. Other risk factors, and chronic renal insufficiency or use of medications, including diuretics, ACE inhibitors, NSAIDs, or angiotensin receptor blocker

Hepatic impairment: Avoid use, there's risk of lactic acidosis.

Renal impairment: eGFR ≥20 mL/min/1.73 m2: No dosage adjustment required.

eGFR <20 mL/min/1.73 m2: Data are insufficient; no dosing recommendations available.

eGFR <30 mL/min/1.73 m2: Not recommended.

Patients on dialysis: Contraindicated

Pregnancy: Limited data available. Avoid use.

Breastfeeding: Avoid use

Adverse effects: Urinary tract infection, dyslipidemia, mycotic infections, constipation.

hypoglycaemia (in combination with insulin orsulfonylurea), hypovolaemia (more common in elderly).

Interactions with other medicines (*indicates serious):

Rifamycins (rifampicin) might decrease the exposure to empagliflozin.

Enalapril

See Enalapril section 14.3.1 Angiotensin-Converting Enzyme Inhibitors

Eplerenone

ATC code: C03DA04

Tablet, 25mg LOU 4

Indications and dose

Adult

Adjunct patients with left ventricular ejection fraction <40% evidence of heart failure, following myocardial infarction (start therapy within 3–14 days of event) : Start with 25 mg daily, then increased to 50 mg daily, increased within 4 weeks of initial treatment.

Adjunct in chronic mild heart failure with left ventricular ejection fraction <30%

Start with 25 mg daily, then increased to 50 mg daily, increased within 4 weeks of initial treatment.

Paediatric: Safety and efficacy not established.

Contraindications:

Elderly For aldosterone antagonists, risk of hyperkalemia with concurrent use of potassium-conserving drugs without monitoring of serum potassium. Hypersensitivity to spironolactone

Precautions: Hyperkalemia, liver dysfunction, metabolic or respiratory acidosis,

Hepatic impairment: Avoid.

Renal impairment: Initially 25 mg on alternate days if creatinine clearance 30–60 mL/minute. Avoid if creatinine clearance less than 30 mL/minute.

Pregnancy: No information available

Breastfeeding: Use if benefits outweigh the risk

Adverse effects: Arrhythmias, asthenia, constipation, syncope, vomiting, angioedema, cholecystitis ,eosinophilia, dizziness, dyslipidaemia, electrolyte imbalance, headache, insomnia, muscle spasms, renal impairment, gynaecomastia, hyperhidrosis, hypothyroidism, postural hypotension.

Interactions with other medicines (*indicates serious): The risk of hyperkalemia is higher in patients with impaired renal function, proteinuria, diabetes and those concomitantly treated with Angiotensin Enzyme Inhibitors,(ACEIs) Angiotensin Receptor Blockers (ARBs), Non-steroidal anti-inflammatory drugs (NSAIDs) and moderate CYP3A inhibitors.

Patients taking moderate CYP3A inhibitors that cannot be avoided should have their dose of eplerenone reduced.

Notes:

» Hypertension: Initial 50 mg per day. May increase to 50 mg every 12hrly; may take up to four weeks for full therapeutic response.

Furosemide

ATC code: C03CA01

Injection, 10 mg/mL (2-mL amp), LOU 4

Tablet, 40 mg (cross-scored), LOU 3

Oral liquid, 20 mg/5 mL, LOU 4

Indications and use

Adult

Oedema associated with heart failure, oral: 40 mg stat in the morning; maintenance 20 mg once a day or 40 mg on alternate days

Oedema associated with heart failure, by IM injection or slow IV injection or IV infusion: Initially 20–50 mg, then increased in steps of 20 mg every 2 hours if required, doses greater than 50 mg given by intravenous infusion only; maximum 1.5 g per day

Paediatric

Oedema in heart failure, oral:

Neonate: 0.5–2 mg/kg every 12–24hours (every 24hours if corrected age under 31 weeks). **Child 1 month – 11 years:** 0.5–2 mg/kg 2–3 times daily, higher doses may be required in resistant oedema, maximum 12 mg/kg (80 mg) daily.

Child 12–17 years: 20–40 mg daily; increased to 80–120 mg daily, in resistant oedema

Oedema in heart failure, by slow IV:

Neonate: 0.5–1 mg/kg every 12–24hours (every 24hours if corrected age under 31 weeks).

Child 1 month – 11 years: 0.5–1 mg/kg (maximum 4 mg/kg) repeated every 8 hours as necessary, maximum 6 mg/kg per day

Child 12–17 years: 20–40 mg every 8 hours as required, higher doses may be required in resistant cases

Oedema in heart failure, by continuous IV infusion:

Child: 0.1–2 mg/kg/hour

Contraindications: renal failure with anuria, precomatose states associated with liver cirrhosis.

Precautions: Monitor electrolytes particularly potassium and sodium, hypotension, prostatic enlargement, the elderly, correct hypovolaemia in oliguria before administration.

Hepatic impairment: Hypokalaemia may precipitate coma (use potassium sparing diuretic to prevent this), increased risk of hypomagnesaemia in alcoholic cirrhosis

Renal impairment, Higher doses may be needed in moderate impairment, monitor for deafness following rapid IV injection. **Pregnancy:** Furosemide should not be used to treat gestational hypertension because of the maternal hypovolaemia associated with this condition.

Breastfeeding: Amount too small to be harmful. May inhibit breastfeeding.

Adverse effects: blood dyscrasias, GIT disturbance, anemia, anorexia, fatigue, allergic reactions, dizziness, headache, hypokalaemia, hypomagnesaemia, hyponatraemia,

hypochloraemic alkalosis (for symptoms of fluid and electrolyte imbalance,

see introductory notes), increased calcium excretion, hypovolaemia, hyperglycaemia (but less often than with thiazide diuretics), temporary increase in plasma cholesterol and triglyceride concentration, hyperuricaemia and gout, bone marrow depression (withdraw treatment), pancreatitis (with large parenteral doses), tinnitus and deafness (deafness may be permanent if other ototoxic drugs taken).

Interactions with other medicines (*indicates serious):

*Amikacin, Amitriptyline,Amphotericin B

Carbamazepine , Chlorpromazine, Cisplatin

Dexamethasone, Diazepam, *Digoxin, *Enalapril

Ethanol, *Gentamicin, Halothane,Hydrochlorothiazide

Hydrocortisone, Ibuprofen, Ketamine, Lidocaine

*Lithium, Nitrous oxide, Prednisolone, Propranolol

*Quinidine, Salbutamol, *Streptomycin, Thiopental

*Vancomycin

Notes: To avoid ototoxicity, IV doses should be given no faster than 0.5 mg/kg per minute (doses <120 mg) or 4 mg/min (doses ≥ 120 mg).

Hydralazine Hcl

See Hydralazine section 14.3.6
Antihypertensive medicines

Isosorbide Dinitrate

See Isosorbide Dinitrate section 14.1
Antianginal medicines

Ivabradine

ATC code: C01EB17

Tablet (scored), 5 mg, LOU 5

Tablet, 7.5 mg, LOU 5

Indications and use

Adult

Angina in patients in normal sinus rhythm, oral: Initially 2.5–5 mg twice daily for 3–4 weeks, then increase if necessary up to 7.5 mg twice daily, dose to be increased gradually, reduced if not tolerated to 2.5–5 mg twice daily; heart rate at rest should not be allowed to fall below 50 beats per minute; discontinue treatment if no improvement in symptoms within 3 months

» **Elderly 75 years and above:** Initially 2.5 mg

Mild to severe chronic heart failure, oral: Initially 5 mg twice daily for 2 weeks, then increase if necessary to 7.5 mg twice daily, reduced if not tolerated to 2.5–5 mg twice daily; heart rate at rest should not be allowed to fall below 50 beats per minute

» **Elderly 75 years and above:** Initially 2.5 mg

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Acute MI, cardiogenic shock, congenital QT syndrome, do not initiate for angina if heart rate below 70 beats per minute, do not initiate for chronic heart failure if heart rate below 75 beats per minute, immediately after cerebrovascular accident, patients dependent on pacemaker, second- and third-degree heart block, severe hypotension, sick-sinus, syndrome, sino-atrial block, unstable angina, unstable or acute heart failure

Precautions: Atrial fibrillation or other arrhythmias (treatment ineffective), elderly, in angina, consider stopping if there is no or limited symptom improvement after 3 months, intraventricular conduction defects, mild to moderate hypotension (avoid if severe), retinitis pigmentosa.

Hepatic Impairment: Use with caution in moderate impairment, avoid in severe impairment due to lacking data.

Renal Impairment: use with caution if eGFR less than 15 mL/min/1.73 m2.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Arrhythmias, atrioventricular block, dizziness, headache, hypertension, vision disorders, pain, angioedema, constipation, diarrhoea, eosinophilia, hyperuricaemia, hypotension, muscle cramps, nausea, QT interval prolongation, skin

Reactions, syncope, vertigo.

Interactions with other medicines (*indicates serious): Drugs affecting metabolism by CYP3A4 (e.g., *erythromycin, *clarithromycin, *fluconazole, *ketoconazole, *voriconazole, *itraconazole, phenytoin, grapefruit juice, *ritonavir, rifampicin, St John's Wort), *imatinib, *diltiazem, *verapamil, *aprepitant

Notes:

- DOSE ADJUSTMENTS DUE TO INTERACTIONS: Reduce initial dose to 2.5 mg twice daily with concurrent use of moderate CYP3A4 inhibitors (except diltiazem, erythromycin and verapamil where concurrent use is contraindicated).
- Monitor regularly for atrial fibrillation (consider benefits and risks of continued treatment if atrial fibrillation occurs). Monitor for bradycardia, especially after any dose increase, and discontinue if resting heart rate persistently below 50 beats per minute or continued symptoms of bradycardia despite dose reduction.

Losartan

See Losartan section 14.3.2 Angiotensin receptor blocker

Metolazone

ATC code: C03BA08

Tablet, 5 mg, LOU 5

Indications and use

Adult

Oedema in congestive heart failure | Oedema in renal disease | Hypertension:

Initially 2.5 mg daily, increased if necessary to 5 mg daily days

Paediatric

Not recommended

Contraindications: Anuria, hypersensitivity to metolazone or sulfonamides, hepatic coma

Precautions: Use with caution with dyslipidemia, hypotension diabetes mellitus, hyperuricemia or gout, systemic lupus erythematosus or liver disease

Hepatic impairment: avoid use in severe impairment.

Renal impairment: Dose adjustments not required if eGFR is less than 30 mL/minute/1.73m2.

Pregnancy: Should not be used in pregnancy

Breastfeeding: Not recommended in breastfeeding

Adverse effects: Azotaemia, glycosuria, hypotension, muscle complaints

Interactions with other medicines (*indicates serious): May aggravate digitalis toxicity, avoid concurrent use with lithium

Milrinone

ATC code: C01CE02

Injection (solution), 1 mg/mL (10 mL), LOU 6

Indications and dose

Short-term treatment of severe congestive heart failure unresponsive to conventional maintenance therapy (not immediately after MI), acute heart failure, including low output states following heart surgery, IV: Initially 50 micrograms/kg, given over 10 minutes, followed by IV infusion 375–750 nanograms/kg/min, usually given following surgery for up to 12 hours or in congestive heart failure for 48–72 hours; maximum 1.13 mg/kg per day

Paediatric

Congestive heart failure, low cardiac output following cardiac surgery, shock, IV infusion

Neonate: Initially 50–75 micrograms/kg, given over 30–60 minutes, reduce or omit initial dose if at risk of hypotension, then by continuous IV infusion 30–45 micrograms/kg/hour for 2–3 days (usually for 12 hours after cardiac surgery)

Child: Initially 50–75 micrograms/kg, given over 30–60 minutes, reduce or omit initial dose if at risk of hypotension, then by continuous IV infusion 30–45 micrograms/kg/hour for 2–3 days (usually for 12 hours after cardiac surgery).

Contraindications: Hypersensitivity to milrinone, Severe hypovolaemia

Precautions: Correct hypokalaemia, heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction.

Hepatic Impairment: No information available

Renal Impairment: Reduce dose and monitor response if eGFR less than 50 mL/min/1.73 m2. the loading dose is not affected, but the infusion rate should be adjusted according to haemodynamic response.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Arrhythmia supraventricular (increased risk in patients with pre-existing arrhythmias), arrhythmias, headache, hypotension, Angina pectoris, hypokalaemia, thrombocytopenia, tremor, Anaphylactic shock, bronchospasm, skin eruption, Renal failure.

Interactions: Digoxin, drugs that can cause hypokalaemia.

Notes:

- Monitor blood pressure, heart rate, ECG, central venous pressure, fluid and electrolyte status, renal function, platelet count and hepatic enzymes.

Nitroglycerine (NTG)

ATC code: C01DA02

Injection, 2.5 mg/mL (10 mL) amp, LOU 5

Indications and dose

Adult

Unresponsive congestive heart failure, including that secondary to acute MI, acute left-sided heart failure, and acute MI, by IV infusion: 20–25 micrograms/min; this may be decreased to 10 micrograms/min or increased in steps of 20–25 micrograms/min every 15–30 minutes until the desired effect is obtained

Refractory unstable angina pectoris and coronary insufficiency, including Prinzmetal's angina, by IV infusion: 10 micrograms/min is recommended with increments of 10 micrograms/min being made at approximately 30-minute intervals

Hypertensive episodes and/or myocardial ischaemia during and after cardiac surgery, by IV infusion: 15–20 micrograms/min, with subsequent increments of 10–15 micrograms/min until the required effect is obtained

Induction of controlled hypotension for surgery, by IV infusion: 25 micrograms/min is recommended to control hypertension or produce hypotension during surgery; this may be increased by increments of 25 micrograms/min at 5 minute intervals until blood pressure is stabilized; doses of 10–200 micrograms/min are usually sufficient during surgery, although doses of up to 400 micrograms/min have been required in some cases

Paediatric

Hypertension during and after cardiac surgery, heart failure after cardiac surgery, coronary vasoconstriction in myocardial ischaemia, vasoconstriction in shock, by continuous IV infusion

Neonate: 0.2–0.5 microgram/kg/min, adjusted according to response, maintenance 1–3 micrograms/kg/min (max. per dose 10 micrograms/kg/min).

Child: Initially 0.2–0.5 microgram/kg/min, adjusted according to response, maintenance 1–3 micrograms/kg/min (max. per dose 10 micrograms/kg/min), maximum 200 micrograms/min.

Contraindications: Acute circulatory failure (shock, collapse), Cardiogenic shock (unless a sufficient end-diastolic pressure is maintained by appropriate measures), severe anaemia, Toxic pulmonary oedema. See Glyceryl trinitrate contraindications section 14.1 Antianginal Medicines for more.

Precautions: Hypothermia, hypothyroidism, Low filling pressures, Orthostatic dysfunction, hypoxaemia. Methaemoglobinaemia has been reported following nitroglycerine infusion, monitor.

Hepatic Impairment: Additional dose adjustments in patients with severe hepatic insufficiency may be necessary and require additional monitoring.

Renal Impairment: Additional dose adjustments in patients with severe renal failure may be necessary and require additional monitoring.

Pregnancy: Not known to be harmful

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: See under Glyceyl trinitrate interactions section 14.1 Antianginal Medicines.

Interactions: See under Glyceyl trinitrate interactions section 14.1 Antianginal Medicines.

Norepinephrine (Noradrenaline)

ATC code: C01CA03

Injection, 1 mg/mL, LOU 5

Indications and dose

Adult

Acute hypotension (initial and on-going treatment), by IV infusion: Initially 0.16–0.33 mL/min, adjusted according to response, dose applies to a solution containing 40 micrograms (base)/mL only, dilute the 1 mg/mL concentrate for infusion for this solution (see notes below)

On-going treatment of acute hypotension (with escalating dose requirements) (body weight 50 kg and above), by IV infusion: Use the 0.08 mg/mL or 0.16 mg/mL solution for infusion (see notes below)

Paediatric

Acute hypotension (septic shock), shock secondary to excessive vasodilation, by continuous IV infusion

Neonate: 20–100 nanograms/kg/min (max. per dose 1 microgram/kg/min), adjusted according to response; dilute the 1 mg/mL concentrate for infusion for this dose

Child: 20–100 nanograms/kg/min (max. per dose 1 microgram/kg/min), adjusted according to response; dilute the 1 mg/mL concentrate for infusion for this dose.

Contraindications: Hypersensitivity to norepinephrine/epinephrine tartrate or to any of the excipients, Hypertension

Precautions: Coronary or mesenteric or peripheral vascular thrombosis, diabetes mellitus, extravasation at injection site may cause necrosis, following MI, hypercapnia, hyperthyroidism, hypoxia, Prinzmetal's, variant angina, susceptibility to angle-closure glaucoma, uncorrected hypovolaemia, elderly.

Hepatic Impairment: No or insufficient data on the pharmacokinetics of this drug in hepatic impairment. Therefore, uptitration should be done with caution.

Renal Impairment: No or insufficient data on the pharmacokinetics of this drug in renal. Therefore, uptitration should be done with caution.

Pregnancy: May reduce placental perfusion and induce foetal bradycardia. It may also exert a contractile effect on the pregnant uterus and lead to foetal asphyxia in late pregnancy therefore use only if potential benefit outweighs risk.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Anxiety, arrhythmias, dyspnoea, extravasation necrosis, headache, hypertension, hypovolaemia, peripheral ischaemia.

Interactions: *Betablockers, e.g., bisoprolol, *ergometrine, volatile halogenated anaesthetic agents, *MAOIs, *linezolid, *tricyclic antidepressants, e.g., amitriptylline, adrenergic-serotoninergic drugs, other cardiac sensitizing agents,

Notes:

- DOSE EQUIVALENCE AND CONVERSION: 1 mg of norepinephrine/epinephrine base is equivalent to 2 mg of norepinephrine/epinephrine acid tartrate. Doses expressed as the base.
- Monitor blood pressure and rate of flow frequently
- DILUTION INSTRUCTIONS: Dilute before use with glucose 5% solution or sodium chloride 9 mg/mL (0.9%) with glucose 5% solution. Either add 2 mL concentrate to 48 mL glucose 5% solution (or sodium chloride 9 mg/mL (0.9%) with glucose 5% solution) for administration by syringe pump or add 20 mL of concentrate to 480 mL glucose 5% solution (or sodium chloride 9 mg/mL (0.9%) with glucose 5% solution) for administration by drip counter. In both cases the final concentration of the infusion solution is 40 mg/L norepinephrine/epinephrine base (which is equivalent to 80 mg/L norepinephrine/epinephrine tartrate). The product is compatible with PVC infusion bags, incompatible with alkalis. Give through a CVC.

Sacubitril + Valsartan

ATC code C09DX04

Tablet (f/c), 24 mg + 26 mg, LOU 5

Tablet (f/c), 48 mg + 52 mg, LOU 5

Indications and dose

Adult

Symptomatic chronic heart failure with reduced ejection fraction (in patients not currently taking an ACEI or angiotensin II receptor antagonist or stabilised on low doses of either of these agents), oral: Initially 24/26 mg twice daily for 3–4 weeks, increased if tolerated to 49/51 mg twice daily for 3–4 weeks, then increased if tolerated to 97/103 mg twice daily

Symptomatic chronic heart failure with reduced ejection fraction (in patients currently stabilised on an ACEI or angiotensin II receptor antagonist), oral: Initially 49/51 mg twice daily for 2–4 weeks, increased if tolerated to 97/103 mg twice daily; consider a starting dose of 24/26 mg if systolic blood pressure less than 110 mmHg.

Paediatric: Safety and efficacy of sacubitril + valsartan in children and adolescents below 18 years have not been established. No data are available.

Contraindication: Concomitant use with an ACEI (do not initiate until at least 36 hours after discontinuing ACEI—risk of angioedema), concomitant use with an angiotensin II receptor blocker (ARB), systolic blood pressure less than 100 mmHg, serum potassium level >5.4 mmol/L, hypersensitivity to the active ingredients of any of the excipients, history of angioedema related to ACEI of ARB therapy, hereditary angioedema, severe hepatic impairment, biliary cirrhosis and cholestasis, 2nd and 3rd trimester of pregnancy.

Precautions: Caution is required in the following, patients with renal artery stenosis (monitoring of renal function is recommended) and patients with New York Heart Association functional classification IV due to limited clinical experience in this population. Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan treatment should be considered.

Hepatic Impairment: No dose adjustment for mild hepatic impairment. Sacubitril/Valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis. No or insufficient data on the pharmacokinetics of this drug in moderate hepatic impairment. Therefore, uptitration should be done with caution.

Renal Impairment: No dose adjustment for mild renal impairment. No or insufficient data on the pharmacokinetics of this drug in moderate and severe renal impairment. Therefore, uptitration should be done with caution. Not recommended in ESRD.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding, No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Anaemia, asthenia, cough, diarrhoea, dizziness, electrolyte imbalance, gastritis, headache, hypoglycaemia, hypotension, nausea, renal impairment, syncope, vertigo.

Interactions with other medicines (*indicates serious): *ACEIs, e.g., enalapril, *ARB, e.g., losartan, *statins, e.g., atorvastatin, Phosphodiesterase 5 inhibitors, e.g., sildenafil, *potassium sparing diuretics, e.g., amiloride, spironolactone, eplerenone, potassium supplements, NSAIMs, selective COX2 inhibitors, *lithium, rifampicin, ciclosporin.

Spironolactone

See Spironolactone section 14.3.6 Other anti-hypertensive

Torsemide

ATC code: C03CA04

Tablet (scored), 10 mg, 20 mg, LOU 5

Indications and dose

Adult

Oedema, oral: 5 mg once daily, to be taken preferably in the morning, then increase if necessary to 20 mg once daily; maximum 40 mg per day

Paediatric: There is insufficient experience in children and adolescents, therefore its use is not recommended unless under specialist supervision.

Contraindications: Renal failure with anuria, hepatic coma and pre-coma, hypotension, pre-existing

hypovolaemia, pregnancy and breastfeeding, hypersensitivity to Torsemide and sulphonylureas, cardiac arrhythmias, simultaneous therapy with aminoglycosides or cephalosporins, or renal dysfunction due to drugs which cause renal damage.

Precautions: Patients with history of gout and difficulty with micturition, e.g., prostatic hypertrophy. Hypokalaemia, hyponatraemia, hypovolaemia and disorders of micturition must be corrected before treatment.

Hepatic Impairment: No or insufficient data on the pharmacokinetics of this drug in hepatic impairment. Therefore, uptitration should be done with caution.

Renal Impairment: Contraindicated in renal failure with anuria or due to nephrotoxic drugs.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Fluid and electrolyte imbalance, Metabolic alkalosis, Headache, Dizziness, Asthenia, fatigue, GI disorder, bladder dilation, urinary retention, Allergic dermatitis, anaemia, cerebral ischaemia, embolism, ischaemic heart disease, MI, pancreatitis, syncope, visual impairment, Thrombocytopenia, Leukopenia, hypotension, hepatic enzyme increased, Muscle spasms.

Interactions: Antihypertensive drugs particularly ACEIs, e.g., ramipril, cardiac glycosides, aminoglycosides, e.g., *amikacin, *gentamycin, platinum compounds, e.g., cisplatin, cephalosporins, digoxin, NSAIMs, e.g., indomethacin, acetylsalicylic acid, probenecid, *lithium, *theophylline, antidiabetic drugs, epinephrine, norepinephrine/epinephrine, mineralo- and glucocorticoids and laxatives.

14.5. Antithrombotic Medicines

14.5.1. Anti-Platelet Medicines

Acetylsalicylic Acid (Aspirin)

ATC code: B01AC06

Tablet, 75 mg, LOU 4

Indications and doses: cardiovascular disease (secondary prevention), unstable angina and MI, suspected and confirmed transient ischaemic attack, ischaemic stroke, atrial fibrillation following a disabling ischaemic stroke, ischaemic stroke in patients receiving anticoagulation for a prosthetic heart valve, post coronary by-pass surgery, pyrexia, pain, inflammation (see section 3.1), migraine (see section 8.1), juvenile joint disease (see section 28.3)

Adult

Cardiovascular disease (secondary prevention), oral: 75 mg daily

Management of unstable angina and non-ST-segment elevation MI, management of ST-segment elevation MI, oral: 300 mg, chewed or dispersed in water

Suspected transient ischaemic attack, oral: 300 mg once daily until diagnosis established

Transient ischaemic attack (long-term treatment in combination with dipyridamole), ischaemic stroke not associated with atrial fibrillation (in combination with dipyridamole if clopidogrel contraindicated or not tolerated), ischaemic stroke not associated with atrial fibrillation (used alone if clopidogrel and dipyridamole contraindicated or not tolerated), oral: 75 mg once daily

Acute ischaemic stroke, oral: 300 mg once daily for 14 days, to be initiated 24 hours after thrombolysis or as soon as possible within 48 hours of symptom onset in patients not receiving thrombolysis

Atrial fibrillation following a disabling ischaemic stroke (before being considered for anticoagulant treatment), oral: 300 mg once daily for 14 days

Following disabling ischaemic stroke in patients receiving anticoagulation for a prosthetic heart valve and who are at significant risk of haemorrhagic transformation, oral: 300 mg once daily, anticoagulant treatment stopped for 7 days and to be substituted with aspirin

Following coronary by-pass surgery, oral: 75–300 mg daily

Paediatric

Antiplatelet, prevention of thrombus formation after cardiac surgery, oral

Neonate: 1–5 mg/kg once daily.

Child 1 month–11 years: 1–5 mg/kg once daily (max. per dose 75 mg)

Child 12–17 years: 75 mg once daily

Kawasaki disease, oral

Neonate: Initially 8 mg/kg 4 times a day for 2 weeks or until afebrile, followed by 5 mg/kg once daily for 6–8 weeks; if no evidence of coronary lesions after 8 weeks, discontinue treatment or seek expert advice.

Child 1 month–11 years: Initially 7.5–12.5 mg/kg 4 times a day for 2 weeks or until afebrile, then 2–5 mg/kg once daily for 6–8 weeks, if no evidence of coronary lesions after 8 weeks, discontinue treatment or seek expert advice..

Contraindications: hypersensitivity (including asthma, angioedema, urticaria, or rhinitis) to acetylsalicylic acid or any other NSAIM, children and adolescents under 16 years (risk of Reye syndrome, see note below), active peptic ulceration, haemophilia and other bleeding disorders, active peptic ulceration, children under 16 years (risk of Reye's syndrome), gout, severe renal and hepatic disease.

Precautions: uncontrolled hypertension, allergic disease, anaemia, asthma, dehydration, elderly, G6PD deficiency, avoid during fever or viral infection in children (risk of Reye's syndrome), previous peptic ulceration, thyrotoxicosis.

Hepatic impairment: Contraindicated in severe impairment. Use with caution in moderate impairment. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Renal impairment: Contraindicated in severe impairment. Use with caution in moderate impairment, sodium and water retention. Monitor renal function. If used in dehydrated patients' acetylsalicylic acid can cause deterioration of renal function.

Pregnancy: Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe. Aspirin should be avoided in late pregnancy and generally during breastfeeding. Use antiplatelet doses with caution during third trimester, impaired platelet function and risk of haemorrhage, delayed onset and increased duration of labour with increased blood loss, avoid analgesic doses, if possible, in last few weeks, high doses may be related to intra-uterine growth restriction, teratogenic effects, closure of foetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of newborn, kernicterus may occur in jaundiced neonates.

Breastfeeding: Avoid—possible risk of Reye's syndrome, regular use of high doses could impair platelet function and produce hypoprothrombinaemia in infant if neonatal vitamin K stores low.

Adverse Effects: bronchospasm, urticaria, Steven-Johnsons syndrome, increased bleeding tendencies e.g. GI haemorrhage, also other haemorrhage (for example, subconjunctival, intracranial haemorrhagic vasculitis), Dyspepsia, Aplastic anaemia, thrombocytopenia, granulocytosis, hepatic failure, hyperuricaemia, renal impairment.

Interactions with other medicines (*indicates serious): *methotrexate, *warfarin, *fluoxetine, *heparin, *ibuprofen, acetazolamide, antacids, dexamethasone, enalapril, hydrocortisone, metoclopramide, mifepristone, phenytoin, prednisolone, spironolactone, valproic acid.

Notes:

- Owing to an association with Reye's syndrome, manufacturer advises aspirin-containing preparations should not be given to children under 16 years, unless specifically indicated, e.g., for Kawasaki disease.

Aspirin + clopidogrel

ATC code:

Tablet, 75mg + 75mg, *LOU 4*

Indications and dose

Adult

Transient ischaemic attack

Ischaemic stroke not associated with atrial fibrillation.

Following coronary by-pass surgery

Prevention of atherothrombotic events in percutaneous coronary intervention

For contraindications, dose adjustments, adverse effects and interactions – see individual monographs.

Clopidogrel

ATC code: B01AC04

Tablet, 75 mg, LOU 4

Indications and dose

Adult

Prevention of atherothrombotic events in percutaneous coronary intervention (adjunct with aspirin), oral: Loading dose 300 mg, to be taken prior to the procedure; alternatively loading dose 600 mg; higher dose may produce greater and more rapid inhibition of platelet aggregation

Prevention of atherothrombotic events in peripheral arterial disease or within 35 days of MI, or within 6 months of ischaemic stroke, oral: 75 mg once daily

Prevention of atherothrombotic events in acute coronary syndrome without ST-segment elevation (given with aspirin), oral: Initially 300 mg, then 75 mg daily for up to 12 months

Prevention of atherothrombotic events in acute MI with ST-segment elevation (given with aspirin), oral

- 18–75 years: Initially 300 mg, then 75 mg for at least 4 weeks
- 76 years and over: 75 mg daily for at least 4 weeks

Prevention of atherothrombotic and thromboembolic events in patients with atrial fibrillation and at least one risk factor for a vascular event (with aspirin) and for whom warfarin is unsuitable, oral: 75 mg once daily

Transient ischaemic attack for patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor, acute ischaemic stroke for patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor, oral: 75 mg once daily

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Active bleeding

Precautions: Discontinue 7 days before elective surgery if antiplatelet effect not desirable, patients at risk of increased bleeding from trauma, surgery, or other pathological conditions, elderly with concurrent significant bleeding risk.

Hepatic Impairment: Use with caution. Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses.

Renal Impairment: No or insufficient data on the pharmacokinetics of this drug in renal impairment. Therefore, use with caution.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: GI disturbance, GI and duodenal ulceration, Haemorrhage (e.g., GI, intracranial), skin reactions, SCARs, thrombocytopenia, Acquired

haemophilia, agranulocytosis, anaemia, arthralgia, arthritis, glomerulonephritis, hallucination, hepatic disorders, hypersensitivity, hypotension, neutropenia, pancreatitis, respiratory disorders, vasculitis, Kounis syndrome.

Interactions with other medicines (*indicates serious): *fluconazole, heparin, NSAIMs, *fluoxetine, *enzalutamide, *grapefruit juice, *pioglitazone, proton pump inhibitors, e.g., omeprazole, rosuvastatin, rifampicin, oral anticoagulants, e.g., warfarin.

14.5.2. Thrombolytic Medicines

Alteplase

ATC code: B01AD0,

Powder for injection, 50 mg, *LOU 5*

Indications and dose

Adults

Acute myocardial infarction, intravenous injection: 10 mg to be initiated within 6–12 hours of symptom onset, followed by (by intravenous infusion) 50 mg, to be given over 60 minutes, then (by intravenous infusion) 10 mg for 4 infusions, each 10mg infusion dose to be given over 30 minutes, total dose of 100mg over 3 hours; maximum 1.5 mg/kg in patients less than 65 kg.

Acute myocardial infarction, accelerated regimen, intravenous injection:

Body weight up to 65 kg: Initially 15 mg, to be initiated within 6 hours of symptom onset, followed by (by intravenous infusion) 0.75 mg/kg, over 30 minutes, then 0.5 mg/kg, to be given over 60 minutes, maximum total dose of 100mg administered over 90 minutes.

Body weight 65 kg and above: Initially 15 mg, to be initiated within 6 hours of symptom onset, followed by (by intravenous infusion) 50 mg to be given over 30 minutes, then 35mg over 60 minutes, maximum total dose of 100mg administered over 90 minutes.

Paediatric: Limited data available for acute myocardial infarction

Contraindications: Recent delivery, Contra-indicated if history of hypersensitivity to gentamicin (residue from manufacturing process).

Active internal bleeding, history of recent stroke, ischemic stroke within 3 months except when within 4.5 hr, bleeding diathesis, aortic dissection, current severe uncontrolled hypertension,

Recent (within 3 months) brain injury or facial trauma intracranial or intraspinal surgery or serious head trauma, presence of aneurysms, current severe uncontrolled hypertension, prior intracranial hemorrhage

Precautions: Use caution in recent major surgery, severe hepatic/renal dysfunction acute pericarditis, hemostatic defects, severe thrombophlebitis, cerebrovascular disease, hypertension

Renal impairment: Dose as in normal renal function

Hepatic impairment: Avoid use in severe impairment.

Pregnancy: To be used if benefit outweighs the risk

Breastfeeding: There are no data on presence of alteplase in human milk

Adverse effects: Hypotension, Intracranial hemorrhage, Pulmonary embolism, Pulmonary edema, Arterial embolism, Bruising, Hypotension, DVT, Intracranial hemorrhage

Interactions with other medicines (*indicates serious): Concurrent use with other anticoagulants should be avoided. Risk of bleeding may increase when combined with cenocoumarol Acenocoumarol. Alclofenac,Aldesleukin,Alemtuzumab Acetylsalicylic acid.

Reteplase

ATC code: B01AD07

Powder for injection, 18 mg/10 ml, LOU 5

Indications and dose

Adults

Acute Myocardial Infarction, Intravenous injection: 10 units IV bolus (over 2 minutes), followed by a second dose given 30 minutes after first (for total cumulative dose of 20 units)

Treatment should be initiated after onset of acute myocardial infarction.

Give each bolus injection via an intravenous line in which no other medication is being simultaneously injected or infused.

Paediatric: No information available

Contraindications: Hypersensitivity, recent cardiovascular event,uncontrolled hypertension,bleeding, recent intracranial or intraspinal surgery or trauma, intracranial neoplasm,

Precautions: recent major surgery, cute pericarditis, hemostatic defects, severe thrombophlebitis, patients on oral anticoagulants, diabetic hemorrhagic retinopathy, elderly

Hepatic impairment: Avoid use in severe dysfunction.

Renal impairment: use with caution in< 10 GFR(ml/min)

Pregnancy: Use with caution,if benefits outweighs the risk

Breastfeeding: Limited information. Not known whether drug crosses into breast milk

Adverse effects: Anemia, cholesterol embolization, gastrointestinal bleeding, Cardiogenic shock,pain intracranial hemorrhage, cardiac reinfarction

Interactions with other medicines (*indicates serious): Concurrent use with other anticoagulants should be avoided.

Tenecteplase

ATC code B01AD11

Injection, 10,000 units (50 mg) tenecteplase with diluent in pre-filled syringe containing 10 mL water for injection, LOU 6

Indications and dose m

Adult

Acute MI with persistent ST elevation or recent left bundle branch block, by IV injection: 30–50 mg (max. per

dose 50 mg, i.e., 10,000 units), dose to be given over 10 seconds and initiated within 6 hours of symptom onset according to body weight (see table 1)

Table 1. Tenecteplase dosing according to body weight

Patient's body weight category (kg)	Tenecteplase dose (units)	Tenecteplase dose (mg)	Corresponding volume of reconstituted solution (mL)
<60	6,000	30	6
≥60 to <70	7,000	35	7
≥70 to <80	8,000	40	8
≥80 to <90	9,000	45	9
≥90	10,000	50	10

Paediatric: No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Hypersensitivity to tenecteplase or any of its excipients or gentamicin (a trace residue from the manufacturing process). If treatment with tenecteplase is nevertheless considered to be necessary, facilities for resuscitation should be immediately available in case of need.

Tenecteplase is contraindicated in the following situations because thrombolytic therapy is associated with a higher risk of bleeding, Significant bleeding disorder either at present or within the past 6 months, Patients receiving effective oral anticoagulant treatment, e.g., warfarin sodium (INR > 1.3), Any history of CNS damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery), Known haemorrhagic diathesis, severe uncontrolled hypertension, Major surgery, biopsy of a parenchymal organ, or significant trauma within the past 2 months (this includes any trauma associated with the current AMI), Recent trauma to the head or cranium, Prolonged cardiopulmonary resuscitation (> 2 minutes) within the past 2 weeks, Acute pericarditis and/or subacute bacterial endocarditis, Acute pancreatitis, Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis, Active peptic ulceration, Arterial aneurysm and known arterial/venous malformation, Neoplasm with increased bleeding risk, Any known history of haemorrhagic stroke or stroke of unknown origin, Known history of ischaemic stroke or transient ischaemic attack in the preceding 6 months, Dementia.

Precautions: Advanced age, i.e., over 75 years. In the following conditions, the risk of tenecteplase therapy may be increased and should be weighed against the anticipated benefits: Systolic blood pressure > 160 mm Hg, Cerebrovascular disease, Recent GI or genitourinary bleeding (within the past 10 days), High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation, any known recent (within the past 2 days) IM injection, Low body weight < 60 kg, Patients receiving oral anticoagulants.

Hepatic Impairment: Contraindicated in severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis. No specific guidance on dose adjustment for mild and moderate dysfunction.

Renal Impairment: No or insufficient data on the pharmacokinetics of this drug in renal impairment. No specific guidance on dose adjustment.

Pregnancy: Limited data on the use of tenecteplase in pregnant women. Tenecteplase is not considered to be teratogenic however the benefit of treatment must be evaluated against the potential risks in case of MI during pregnancy.

Breastfeeding: Avoid breastfeeding for 24 hours after dose (express and discard milk during this time).

Adverse effects: Anaphylaxis, drowsiness, hemiparesis, venous thrombosis, haemorrhage, reperfusion arrhythmias, embolism, epistaxis, ecchymosis,

The following have been reported as sequelae of MI and/or thrombolytic administration, hypotension, angina, recurrent ischaemia, cardiac failure, MI, cardiogenic shock, pericarditis, pulmonary oedema, cardiac arrest, mitral valve incompetence, pericardial effusion, cardiac tamponade, myocardial rupture, pulmonary embolism.

Interactions: Bleeding risk increased by concomitant use with medicinal products that affect coagulation or those that alter platelet function, e.g., clopidogrel, Low Molecular Weight Heparin (e.g, enoxaparin), GPIIb/IIIa antagonists.

14.6. Lipid-Lowering Agents

Atorvastatin

ATC code: C10AA05

Tablet, 20 mg, 40 mg, LOU 4

Indications and dose

Adult

Primary cholesterolaemia or combined (mixed) hyperlipidemia in patients who have not responded adequately to diet and other measures: Usual dose is 10 mg once daily, increased if necessary up to 80 mg once daily; dose to be increased at intervals of at least 4 weeks

Heterozygous/homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures: 10 mg once daily, then increased to 40 mg once daily; dose to be increased at intervals of at least 4 weeks; maximum dose is 80 mg per day

Primary prevention of cardiovascular events in patients at high risk of a first cardiovascular event: 20 mg once daily, dose can be increased if necessary

Secondary prevention of cardiovascular events: 80 mg once daily

Paediatric

Hyperlipidaemia including familial hypercholesterolaemia

Child 10–17 years: Initially 10 mg once daily, then increase if necessary up to 20 mg once daily; dose to be adjusted at intervals of at least 4 weeks

Homozygous familial hyperchlorestolaemia

Child 10–17 years: Initially 10 mg once daily, then increase if necessary up to 80 mg once a day; dose to be adjusted at intervals of at least 4 weeks

Contraindications: Hemmorhagic stroke, known hypersensitivity to the drug or any of its excipients, Active liver disease or unexplained persistently raised serum-aminotransferase concentrations > 3 times upper limit of normal (ULN), Creatinine Kinase level >5 times ULN.

Precautions: patients with pre-disposing factors for rhabdomyolysis. Check Creatinine Kinase levels where possible for patients who have renal impairment, hypothyroidism, personal of familial history of muscular toxicity, past history of liver disease or alcoholism, elderly, haemorrhagic stroke.

Hepatic Impairment: Use with caution

Renal Impairment: Dose adjustments: In CKD, for primary and secondary prevention of cardiovascular events [unlicensed starting dose in primary prevention, unlicensed in secondary prevention], initially 20 mg once daily, increased, if necessary (on specialist advice if eGFR <30 mL/min/1.73 m2), max. 80 mg once daily.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse Effects: GI disturbance, rhabdomylosis, muscle rupture, Myalgia associated with muscle stiffness or weakness, elevations of creatine kinase and serum transaminase, hepatitis, headache, skin rash, peripheral neuropathy, hypersensitivity, urinary tract infections, myopathy, sinusitis, epistaxis, hyperglycaemia, joint disorders, pharyngolaryngeal pain, nasopharyngitis, pain, decreased appetite, chest pain, hypoglycaemia, vision disorders, hearing loss, SCARs.

Interactions with other medicines (*indicates serious): CYP3A4 inhibitors (e.g., *ciclosporin, *clarithromycin, *ketoconazole, *voriconazole, *itraconazole, *fluconazole, *ritonavir, *erythromycin), CYP3A4 inducers (e.g., efavirenz, rifampicin, St. John's wort) antacids, bile acid sequestrants, warfarin, oral contraceptives, digoxin, alcohol, cholestyramine, *fibrates, propanolol, amiodarone, *diltiazem *verapamil, *danazole, *imatinib, colchicine.

Notes:

» Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.

15. Dermatological Medicines (Topical)

15.1. Antifungal Medicines

Clotrimazole

ATC code: D01AC01

Cream, 1%, LOU 2

Indications and dose

Adult

Fungal skin infections: Apply topically 2 or 3 times daily for 2 to 4 weeks

Paediatric

Fungal skin infection

Child, all ages:

Apply 1% cream 2–3 times a day

Pregnancy: Minimal absorption from skin, not known to be harmful.

Adverse Effects:

Local reactions including irritation and a burning sensation may occur

Contact allergic dermatitis has been reported.

Miconazole

ATC code: D01AC02

Cream or ointment, 2% (nitrate), LOU 3

Indications and dose

Adult

Superficial fungal infections due to dermatophytes and yeasts, and secondary infections caused by Gram-positive cocci, including ringworm, intertrigo, candida napkin rash, paronychia, and pityriasis versicolor

Skin infections: Apply directly to clean, dry lesions twice daily, continuing for at least 10 days after the condition has cleared

Nail infections: Apply directly to the affected area 1–2 times daily

Paediatric

Superficial fungal infections due to dermatophytes and yeasts, and secondary infections caused by Gram-positive cocci, including ringworm, intertrigo, candida napkin rash, paronychia, and pityriasis versicolor

Child all ages:

Topical: Apply twice daily to clean, dry lesions, continuing for at least 10 days after the condition has cleared

Nail infections: Apply directly to the affected area 1–2 times daily

Hepatic impairment: Dose reduction not required.

Renal impairment: Dose reduction not required.

Adverse effects: Occasional local irritation and burning, stinging, itch, contact dermatitis, discontinue if sensitization occurs.

Rare Allergic reactions.

Interactions with other medicines (*indicates serious): None known

Notes:

- Continue using the treatment for 10 days after symptoms have gone.
- Interactions with other medicines may occur rarely with miconazole as some absorption occurs from topical products.

Terbinafine

ATC code: D01AE15

Cream, 1% (as HCl), LOU 4

Indications and dose

Adult

Tinea Pedis, topical: Apply to affected area twice daily until significant clinical improvement (no more than 4 weeks).

Tinea Corporis & Cruris: Apply once a day for 1 week (no more than 4 weeks).

Paediatric: Use and dose must be determined by doctor

Precautions: Hypersensitivity reactions

Adverse effects: Burning, irritation, or itching at the application site may occur. If any of these effects persist or worsen, notify your doctor or pharmacist promptly.

Interaction: No information of any interactions.

15.2. Anti-Infective Medicines

Fusidic Acid

ATC code: D06AX01

Ointment, 2% (15 g), LOU 4

Indications and dose

Adult

Alone or in combination with systemic therapy for primary and secondary skin infections caused by sensitive strains of Staphylococcus aureus, Streptococcus spp., and Corynebacterium minutissimum, such as impetigo contagiosa, superficial folliculitis, sycosis barbae, paronychia and erythrasma, infected eczematoid dermatitis, infected contact dermatitis, and infected cuts/abrasions

Uncovered lesions: Apply gently 3 or 4 times daily for 1 week

Covered lesions: Less frequent applications may be adequate.

Paediatric dose: Same as adult

Use in pregnancy/breastfeeding: Topical fusidic acid can be used during pregnancy. Do not apply on or near breast if breastfeeding.

Adverse effects: Pain, stinging, burning sensation or redness of skin on application, Skin rashes, dermatitis, Skin itching or redness.

Notes:

» Use **RESTRICTED** to <14 days. Sodium fusidate cream 2% may also be used

Mupirocin

ATC code: D06AX09

Ointment, 2% (15 g), LOU 4

Indications and dose

Adult

Secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm2 in area) due to susceptible isolates of Staphylococcus aureus (S. aureus) and Streptococcus pyogenes (S. pyogenes): Apply a small amount of cream with a cotton swab or gauze pad to the affected area 3 times daily for 10 days.

Paediatric

Secondarily infected traumatic skin lesions

Child younger than 3 months: Use and dose must be determined by doctor

Child 3 months and older: Apply 3 times a day for 10 days.

Impetigo

Child younger than 2 months: Use and dose must be determined by doctor

Child 2 months and older: Apply three times a day.

Adverse effects: Headache, rash, nausea, abdominal pain, burning at the application site, severe bacterial skin infection (cellulitis), skin inflammation, dizziness, itching, secondary wound infection, and mouth sores

Precautions: Do not apply mupirocin cream concurrently with any other lotions, creams or ointments.

Drug interaction: None known

Notes:

» Safety and effectiveness of mupirocin cream have not been established in children younger than 3 months of age, and mupirocin ointment in children younger than 2 months of age

Silver Sulfadiazine

ATC code: D06BA01

Cream, 1% (50 g, 250 g), LOU 2

Indications and dose

Adult

Prophylaxis and treatment of infection in burns, topical: Apply using aseptic technique daily (more frequent if volume of exudate is large) as long as there is possibility of infection or until healing is complete; apply daily every 12 hours to burn to a thickness of approximately 1/16 inch.

Paediatric

Prophylaxis and treatment of infection in burns, topical

Infants under 2 months: Contraindicated

Child over 2 months: Same as adults

Contraindications: Hypersensitivity to sulfonamides, pregnancy, < 2 months age.

Precautions: Renal or hepatic impairment, large areas, G6PD deficiency.

Hepatic impairment: Severe: use with caution.

Renal impairment: Use with caution in patients with impaired renal function, particularly those receiving treatment for extensive burns.

Adverse effects: Common -Pain, rash, burning, itching.

Rare: Necrosis of skin, erythema multiforme, skin discoloration due to deposition of silver, transient neutropenia, transient leukopenia, development of bacterial resistance, hypersensitivity reactions, argyria and sulfonamide induced systemic toxicity.

Interactions with other medicines:

When used over large areas of skin, plasma sulfadiazine concentrations may approach therapeutic levels and when this occurs the interactions below apply.

Sulfadiazine can cause nephrotoxicity, administration with other nephrotoxic drugs may result in additional renal adverse effects.

Sulfadiazine is a folate antagonist and will add to the effects on bone marrow of other folate antagonists, e.g., pyrimethamine.

Ciclosporin: sulfadiazine may decrease ciclosporin concentration and efficacy, monitor ciclosporin concentration and adjust dose as necessary.

Hexamine hippurate: hexamine requires low urine pH for effect, there is an increased risk of crystalluria with sulfonamides as they are poorly soluble at low pH, avoid combination.

Phenytoin: sulfadiazine inhibits metabolism of phenytoin, increasing its concentration and risk of adverse effects, monitor phenytoin concentration and for adverse effects, decrease phenytoin dose if necessary.

Notes:

» WHO age/weight restriction: > 2 months.

» Use with caution if allergic to sulfonamides or the preservative agent used, e.g., chlorhexidine.

» Owing to the association of sulfonamides with severe blood and skin disorders, treatment should be stopped immediately if blood disorders, or rashes develop.

» Leukopenia developing 2–3 days after starting treatment of burns patients is reported usually to be self-limiting and silver sulfadiazine need not be discontinued, provided blood counts are monitored carefully to ensure return to baseline within a few days.

» Argyria may also occur if large areas of skin are treated (or if application is prolonged).

» Some preparations may contain chlorhexidine 0.2%.

- Apply with sterile gloved hands or spatula in a 3–5 mm layer. Whenever, necessary, the cream should be reapplied to any areas from which it has been removed by patient activity. Administration may be accomplished in minimal time because dressings are not required. However, if individual patient requirements make dressings necessary, they may be used.
- Chlorhexidine (caution) is inactivated by anionic agents such as soap, do not use together.
- Silver sulfadiazine may inactivate enzymatic debriding agents.
- Plasma sulfadiazine concentrations may approach therapeutic levels with adverse effects and interactions as for sulfonamides if large areas of skin are treated.

15.3. Anti-Inflammatory and Antipruritic Medicines

Betamethasone

ATC code: D07AC01

Cream and ointment, 0.1% (as valerate), LOU 4

Indications and dose:

Adult

Severe inflammatory skin conditions: Apply sparingly to the affected area, 1–2 times daily until improvement occurs, then less frequently.

Paediatric: Apply a small quantity to the affected area one or two times daily.

Contraindications: Untreated skin infections, broken skin, rosacea, acne, perioral dermatitis, viral skin lesions, widespread plaque psoriasis.

Precautions: Children (avoid prolonged use and use under specialist supervision), psoriasis (may precipitate severe pustular psoriasis on withdrawal), adrenal suppression if used on a large area of the body or for a long time, particularly with an occlusive dressing, use on the face or groin, secondary infection requires treatment with an appropriate antimicrobial.

Use of more than 100 g per week of 0.1% preparation likely to cause adrenal suppression.

Hepatic impairment: Dose reduction not required.

Renal impairment: Dose reduction not required.

Adverse effects: Common: Folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, dilatation of superficial blood vessels, formation of striae, purpura, depigmentation, telangiectasia, acneiform eruptions at site of application.

Allergic contact dermatitis.

Rare: Hyperaesthesia, SC tissue atrophy, hypertrichosis, systemic effects (growth retardation, hypothalamic-pituitary-adrenal axis suppression with prolonged or widespread use (particularly under occlusion), hyperglycaemia, Cushing syndrome, cataract, glaucoma).

Interactions with other medicines: Use of topical corticosteroids is less likely to result in Interactions with other medicines than systemic use, but interactions may occur rarely.

Notes:

- Occlusive, wet dressings (never plastic) may be used if condition is severe.
- Tachyphylaxis may occur. Use minimum amount necessary to control symptoms. Intermittent use (i.e., 2 days on, 2 days off) may at times be appropriate.
- Consider bone mineral density assessment for children receiving large and long-term doses of topical corticosteroids. Use the smallest amount for the shortest period of time to avoid adverse effects. Reduce use once improvement occurs. Discontinue use once control is achieved. Reassess diagnosis if no improvement is seen within 2 weeks. Dermatologist consultation advisable if using on the face.
- WHO age/weight restriction: hydrocortisone preferred in neonates.
- Cream: used for early management of skin conditions
- Ointment: used for management of longer lasting conditions.

Calamine Lotion

ATC code: D04AX

Lotion, 15%, LOU 1

Indications and dose

Adult

Mild pruritus caused by sunburn and other minor skin conditions: Apply liberally to the entire affected area 3–4 times daily with a pad of cotton wool.

Paediatric

Mild pruritus caused by sunburn and other minor skin conditions

Apply liberally 3–4 times daily with a pad of cotton wool.

Contraindications: Hypersensitivity to the active substance(s) or to any of the components.

Precautions: Avoid contact with eyes, Do not use on open wounds or burns.

Hepatic impairment: Dosage reduction not needed.

Renal impairment: Dosage reduction not needed.

Adverse effects: Occasional hypersensitivity or irritant reactions

Interactions with other medicines (*indicates serious):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

- Shake bottle well before use.
- Calamine preparations are of little value for the treatment of insect stings or bites.

Clobetasol Propionate

ATC code: D07AD01

Ointment, 0.05% w/w, LOU 4

Indications and dose

Adult

Short-term treatment only of severe resistant inflammatory skin disorders, psoriasis: Apply thinly 1–2 times a day for up to 4 weeks; maximum 50 g of 0.05% preparation per week

Paediatric: Apply thinly 1–2 times a day for up to 4 weeks

Contraindications: Hypersensitivity to any of the components, children less than 1 years of age, treatment of rosacea, acne vulgaris, perianal and genital pruritis, untreated skin infections or broken skin, pregnancy category C.

Precautions: avoid prolonged use in children, occlusive dressings increase penetration into keratinized lesions; occlusive dressing should be used only at night and for no longer than 2 days.

Adverse Effects: Pruritus, local skin burning and pain.

Interactions: No known interaction with other drugs.

Crotamiton

ATC code: D04AX02

Cream, 10% (30 g) LOU 2

Indications and dose

Adult

Pruritus (including pruritus after scabies): Apply 2–3 times a day.

Paediatric

Pruritus (including pruritus after scabies) (to the skin)

Child 1 month–2 years (on doctor's advice only): Apply once daily.

Child 3–17 years: Apply 2–3 times a day.

Contraindications

Acute exudative dermatoses

Hypersensitivity to the active substance or to any of the excipients

Precautions

Avoid use in buccal mucosa. Avoid use near eyes. Avoid use on broken skin. Avoid use on very inflamed skin. Use on doctor's advice for children under 3 years.

Pregnancy: No information available.

Breastfeeding: No information available, avoid application to nipple area.

Adverse Effects

The most commonly reported adverse reaction during treatment is pruritus. Contact dermatitis and hypersensitivity reactions like rash, eczema, erythema, skin irritation and angioedema may occur rarely.

Hydrocortisone

ATC code: D07AA02

Cream /ointment, 1% (acetate), LOU 3

Indications and dose

Adult

Inflammatory skin conditions: Apply sparingly to the affected area, 1–2 times daily until improvement occurs, then less frequently.

Paediatric: Same as adult dose

Contraindications: Untreated skin infections, broken skin, rosacea, acne, perioral dermatitis.

Precautions: Children (avoid prolonged use), occlusive dressings increase penetration into keratinized lesions, secondary infection requires treatment with an appropriate antimicrobial.

Renal impairment: No dose reduction required. Hepatic impairment: No dose reduction required.

Adverse effects: When used according to directions on small area of skin, adverse effects do not usually occur.

Common: Folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, dilatation of superficial blood vessels, formation of striae, purpura, depigmentation, telangiectasia, acneiform eruptions at site of application, Allergic contact dermatitis.

Rare: Hyperaesthesia, SC tissue atrophy, hypertrichosis, systemic effects (growth retardation, hypothalamic-pituitary-adrenal axis suppression with prolonged or widespread use (particularly under occlusion), hyperglycaemia, Cushing syndrome, cataract, glaucoma)

Notes:

- Interactions do not generally apply to hydrocortisone used for topical application.
- Tachyphylaxis to topical treatment may occur, therefore best used intermittently once control is achieved. Consider bone mineral density assessment for children receiving large and long-term doses of topical corticosteroids or any child supplemented with oral corticosteroids. Topically, hydrocortisone is a mild corticosteroid.

Mometasone

ATC code: D07AC13

Ointment (as furoate), 0.1%, LOU 4

Indications and dose

Adult

Severe inflammatory skin disorders, such as eczema, unresponsive to less potent corticosteroids and psoriasis, to the skin: Apply thinly once daily; to scalp, in case of lotion

Paediatric

Severe inflammatory skin disorders, such as eczema, unresponsive to less potent corticosteroids and psoriasis, to the skin:

Child below 2 years: Not recommended for use due to insufficient data on safety

Child 2–17 years: Apply thinly once daily; to scalp in case of lotion

Contraindications and precautions:

Hypersensitivity, primary infectious ulcers, acne vulgaris. Pregnancy, breastfeeding, children, old age. Avoid in patients with active local infections, known hypersensitivity.

Not licensed for use in children under 2 years.

For external use only. Do not use in or around the eye.

Adverse effects: Burning, tingling, pruritis, when applied over large areas, over abraded or in occlusive dressing can lead to systemic absorption with adrenal suppression.

Patient information: Used with caution in dressing over large areas or in occlusive dressing. If there is irritation discontinue use.

Interactions: Azole antifungals (itraconazole, ketoconazole, voriconazole), Cobicistat, HIV-protease inhibitors, Idelalisib, Macrolides (clarithromycin) increase exposure.

Tacrolimus

ATC code: D11AH01

Ointment, 0.03% (as monohydrate) (10 g), LOU 4

Ointment, 0.1% (as monohydrate) (10 g), LOU 4

Indications and dose

Adult

Atopic dermatitis, 0.03% or 0.1% ointment: Apply thin layer to affected area q12hr, discontinue when symptoms have cleared; if no improvement within 6 weeks, reassess diagnosis

Paediatric

Atopic dermatitis

Child <2 years old: Not recommended

Child 2–15 years, 0.03% ointment: Apply thin layer to affected area q12hr

Child >15 years: Apply 0.03% or 0.1% ointment as thin layer to affected area q12hr; discontinue when symptoms have cleared; if no improvement within 6 weeks, reassess diagnosis

Contraindications: Hypersensitivity reactions and in children below 2 years

Precautions:

Preferably use as second-line agents for short-term and intermittent treatment in unresponsive to, or intolerant of other treatments, Do not use with occlusive dressings, May be associated with development of lymphadenopathy, Not for application in areas with active viral or bacterial infections, Acute renal failure reported (rare)

Potential risk of lymphoma and skin cancer, Not recommended in patients having skin conditions with a skin barrier defect where there is the potential for increased systemic absorption of tacrolimus (e.g., Netherton's syndrome, lamellar ichthyosis, generalized erythroderma, cutaneous graft vs host disease)

Pregnancy and breastfeeding:

Pregnancy Category: C

Breastfeeding: Not known whether tacrolimus is distributed in milk following topical administration to skin

Adverse effects: Skin burning, stinging, redness or soreness, tingling skin, increased sensitivity of the skin to hot or cold temperatures, itching, acne, swollen or infected hair follicles, headache, muscle or back pain.

Commonest: Burning sensation, Pruritus, Flu-like symptoms, Skin erythema, Headache, Seizures, Bullous impetigo, osteomyelitis, septicemia, Lymphomas, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Acute renal failure in patients with or without Netherton's syndrome, renal impairment Rosacea, application site edema

Interactions: Topical drug interaction studies with tacrolimus ointment have not been conducted.

15.4. Medicines Affecting Skin Differentiation & Proliferation

Benzoyl Peroxide

ATC code: D10AE01

Gel, 5% (30 g), LOU 4

Indications and dose

Adult

Mild to moderate acne, adjunct to oral therapy in more severe cases: Use on affected area(s) of skin one to four times a day

Paediatric

Mild to moderate acne, adjunct to oral therapy in more severe cases

Child, topical: Initially apply to clean skin on alternate days, increasing frequency to one to two times daily as tolerance to irritant effect develops.

Child 12 years of age and over: Dosage similar to adults

Precautions: Avoid contact with eyes, mouth, and mucous membranes, avoid use of occlusive dressings, avoid excessive exposure to sunlight, may bleach fabrics, hair and skin.

Hepatic impairment: Dose reduction not required.

Renal impairment: Dose reduction not required.

Adverse effects: Common Initial irritation but subsides with continued use (in some cases may need to reduce frequency or temporarily suspend use), skin dryness or peeling, feeling of warmth, mild stinging or erythema.

Rare Contact sensitivity occurs, occasionally even one application can cause severe irritation.

Interactions: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

- If acne does not respond after 2 months, then use of a topical antibacterial should be considered.
- Cleanse skin before applying and gently pat dry.
- Apply a thin layer to the affected area and rub in gently. Wash hands after application.
- Avoid contact with eyes, lips and other sensitive areas.
- Avoid contact with hair and coloured fabric as bleaching or discoloration may occur.
- Children younger than 12 years of age—Use and dose must be determined by the doctor.

Dithranol

ATC code: D05AC01

Paste, 2%, LOU 4

Indications and dose

Adult

Moderately severe psoriasis (initiate under medical supervision): Start with lower strength preparation (0.1%); carefully apply directly to lesions only, leave in contact for 30 minutes, then wash off thoroughly; repeat application daily, gradually increasing strength to 2% and contact time to 60 minutes at weekly intervals; some 0.1–0.5% strength preparations are suitable for overnight use.

Paediatric: Safety and efficacy not established

Contraindications: Hypersensitivity, avoid use on face, acute eruptions, excessively inflamed areas.

Precautions: irritant (avoid contact with eyes and healthy skin).

Adverse effects: local irritation, excessive erythema or spread of lesions

(Discontinue use): conjunctivitis following contact with eyes, staining of skin, hair, and fabrics.

Note: Wash hands thoroughly after use.

Podophyllin Resin

ATC code: D06BB04

Solution, 15% (in benzoin tincture) (15 mL), LOU 3

Indications and dosage

Adult

Management of warts (external anogenital and plantar) and keratosis: Apply carefully to warts, avoiding contact with normal tissue; use 1 drop at a time allowing drying between drops until area is covered; total volume should be limited to <0.5 mL per treatment session; rinse off after 1–6 hours; may be repeated at weekly intervals but no more than 4 times in all; only a few warts should be treated at any one time

Paediatric

Safety and efficacy have not been established by the manufacturer; however, the CDC recommends the application should be limited to <0.5 mL of podophyllin for an area <10 cm2 of warts per session.

Infants: Safety and efficacy not established.

Contraindications: pregnancy and breastfeeding, and children.

Precautions: avoid use on large areas, very irritant to eyes (keep away from face), avoid contact with normal skin, mucus membranes, and open wounds.

Adverse effects: pruritus. Systemic effects resulting from cutaneous absorption include nausea, vomiting, abdominal pain and diarrhea, also, transient leukopenia and thrombocytopenia, renal failure, delayed neurotoxicity including visual and auditory hallucinations, delusions, disorientation, confusion, and delirium following excessive application.

Interactions: No Interactions with other medicines of clinical significance have been noted

Note:

- Although there is no specific information comparing use of topical podophyllum in children with use in other age groups, this medicine is not expected to cause different Adverse effects or problems in children than it does in adults.
- Must be applied by a trained health-care professional.

Salicylic Acid

ATC code: D01AE12

Ointment, 3%, LOU 4

Indications and dose

Adult

Hyperkeratotic conditions, including common wart, excluding on the face; adjunct in treatment of psoriasis, fungal infections, seborrheic dermatitis, ichthyosis, acne vulgaris, insect bites, burns, and complications associated with pyoderma: Apply directly to the affected area once daily, starting with lower strength preparations; gradually increase strength until a satisfactory response is obtained.

Paediatric

Child under 2 years: Safety and efficacy not established

Child over 2 years: Apply once daily, starting with lower strength preparations, gradually increase strength until satisfactory response obtained

Contraindications: patients hypersensitive to topical polyethylene glycols, broken or inflamed skin, children under 2 years.

Precautions: significant peripheral neuropathy, patients with diabetes at risk of neuropathic ulcers, avoid contact with eyes, mouth, and mucous membranes, avoid application to large areas.

Adverse effects: stinging, local irritation, dermatitis,

salicylism on excessive application or treatment of large areas, particularly in children.

Interactions: No Interactions with other medicines of clinical significance have been noted.

Note:

- Protect surrounding skin, rub warts gently with file or pumice stone once weekly.
- Storage: at room temperature, in tight containers.

Tretinoin cream

ATC code: D10AD

Cream, 0.05%, Lou 4

Indications and dosage

Adult and adolescents (> 12years)

Treatment of acne vulgaris with comedones, papules or pustules. Apply pea-sized amount once daily on face at bedtime after washing with mild soap and drying.

Elderly (>65years)

Safety not established

Paediatrics

Children below 12 years

Not recommended. Safety not established.

Contraindications: Pregnancy, women planning a pregnancy, breastfeeding, patients with a history of hypersensitivity to the active substance or excipient in the product, patients with personal or familial history of skin cancer, patients with pustular and deep cystic nodular acne varieties (acne conglobate and acne fulminans).

Precautions:

- Avoid contact with mouth, eyes, mucous membranes and broken or eczematous skin.
- Avoid frequent application as severe irritation may occur.
- Avoid application at the same time with other topical preparations including cosmetics.

Adverse effects: Peeling, dry skin, burning and stinging, erythema, pruritus, sunburns, increased photosensitivity

Notes

- Avoid exposure to sunlight.
- Use of sunscreens (SPF 30 and above) is recommended.

15.5. Scabicides And Pediculicides

Benzyl Benzoate

ATC code: P03AX01

Lotion, 25% (50 mL), LOU 2

Benzyl benzoate is a representative parasiticide. Various medicines can serve as alternatives.

Indications and dose

Adult

Scabies: Apply from neck down at night for 2 nights; on each occasion wash off after at least 24 hours. A single treatment is usually effective but, if necessary, may be repeated after 1 week.

Pediculosis (lice): Apply to affected area and wash off 24 hours later; further applications possibly needed after 7 and 14 days.

Paediatric

Scabies, topical

Child over 2 years: Apply over whole body with a brush (except for face and head); repeat without bathing on the following day and wash off 24 hours later. A third application may be needed in some cases.

Head, body, and pubic lice, topical

Child over 2 years: Apply to affected area and wash off 24 hours later. Further applications are possibly needed after 7 and 14 days.

Precautions: do not use on inflamed or broken skin, avoid contact with eyes and mucous membranes, not recommended for children, breastfeeding (withhold during treatment).

Avoid contact with face, eyes, mucous membranes and urethral meatus. Do not apply to inflamed skin or weeping surfaces, not recommended for children, breastfeeding (withhold during treatment).

Adverse effects: slight local irritation, transient burning sensation, occasionally rashes. Frequent use causes contact dermatitis.

Interactions: No Interactions with other medicines of clinical significance have been noted

Notes:

- Not for use in children (use Crotamiton)
- Dilute with an equal amount of water for children (12.5%), and 1 part with 3 parts of water for infants (6%).
- **Storage:** At room temperature, in airtight, light resistant containers. Protect from heat.

Calamine Lotion

ATC code: D04AX

Lotion, 15%, LOU 1

Refer to Calamine Lotion Section 15.3

Crotamiton

ATC code: D04AX02

Cream,10% cream, Lou2

Refer to Crotamiton Section 15.3

15.6. Medicines For Jiggers

Benzyl Benzoate Lotion

ATC code: P03AX01

Lotion, 25%, LOU 2

Indications and dose

Adult

Scabies, topical: Apply over the whole body; repeat without bathing on the following day and wash off 24 hours later; a third application may be required in some cases

Paediatric

Scabies, topical

Child over 2 years: Apply over whole body with a brush (except for face and head); repeat without bathing on the following day and wash off 24 hours later. A third application may be needed in some cases.

Head, body, and pubic lice

Child over 2 years: Apply to affected area and wash off 24 hours later. Further applications are possibly needed after 7 and 14 days.

Precautions: Do not use on inflamed or broken skin, avoid contact with eyes and mucous membranes.

Hepatic impairment: Dose reduction not required.

Renal impairment: Dose reduction not required.

Adverse effects: Local irritation, particularly in children.

Interactions: No Interactions with other medicines of clinical significance have been noted.

Notes:

- Can be irritant, especially in patients with eczema, so perform a 10-minute patch test prior to body application.
- Bathing in hot water prior to application is no longer recommended as it may increase absorption and toxicity.
- Scabies itch is often worse in first 24 hours. Avoid eye contact.
- Thoroughly clean all clothing and bed linen.
- Exclude treated patients from contact
- WHO age/weight restriction: > 2 years.
- Not the treatment of choice for scabies. Permethrin is preferred.

White Soft Paraffin (Petroleum Jelly)

ATC code: D02AC (for soft paraffin)

Topical application, 100 g, LOU 1

(Lanolin, cetyl alcohol, glycerin, and petrolatum)

Indications and dose

Adult

Tungiasis: Occlusive petrolatum suffocates the organism; 20% salicylated petroleum jelly (Vaseline) applied 12–24 hours may be more effective in profound infestations. These treatments do not remove the flea from the skin, and they do not result in quick relief from painful lesions. Manual removal has to be done.

Paediatric: Same as adult

Adverse Reactions : A very serious allergic reaction to this drug is rare.

Interaction: No Interactions with other medicines of clinical significance have been noted.

15.7. Sunscreen Preparations

Sun Screening Agents

ATC code: D02BA

Cream or lotion, SPF 50+ (with UVA), LOU 1

Indications and dose

Adult

Photoprotection for those with albinism: Apply liberally every two hours when in the sun.

Paediatric

Infants under 6 months: Should be kept out of the sun. Sunscreen agents should not be used on infants under 6 months because of increased chance of adverse effects. Lotion sunscreen products are preferred for use in children.

Child 6 months old and older: Should be kept out of the sun or have limited exposure; sunscreen agents with an SPF of at least 15 or higher should be applied during exposure to the sun.

Precautions: Do not use sunscreen agents on infants younger than 6 months of age. Avoid using alcohol-based sunscreen products for this age group.

If rash or irritation develops, stop using the sunscreen and check with your doctor.

Sunscreen agents containing aminobenzoic acid, lisadimate, padimate O, or roxadimate may discolor and stain light-colored fabrics yellow.

In addition to using sunscreen agents, it is advisable to minimize exposure to the sun from 10 a.m. to 2 p.m. (11 a.m. to 3 p.m. daylight savings time) when the sun is at its strongest.

Take extra precautions also on cloudy or overcast days and around reflective surfaces such as concrete, sand, snow, or water, since these surfaces can reflect the sun's damaging rays.

Wear protective clothing including a hat, long-sleeved shirt, and long pants. Sunglasses also should be worn to avoid sun damage to the eyes (cataract formation). Avoid sunlamps and tanning parlors because these can damage the skin and eyes as direct sunlight can.

Adverse Reactions: Acne, burning, itching, or stinging of the skin, early appearance of redness or swelling of the skin, late appearance of rash with or without weeping blisters that become crusted, especially in sun-exposed areas, and may extend to unexposed areas of the skin, pain in hairy areas, pus in the hair follicles and drying or tightening of the skin among others.

Interaction: No Interactions with other medicines of clinical significance have been noted.

16. Diagnostic Agents

16.1. Ophthalmic Diagnostics

Fluorescein

ATC code: S01JA01

Test strip, 0.6 mg, LOU 4

Indications and dose

Adult

Corneal abrasions, ulcers, and foreign bodies: Moisten strip with sterile water, saline, or ophthalmic fluid. Touch conjunctiva or fornix with tip of strip until adequately stained.

Paediatric

Corneal abrasions, ulcers, and foreign bodies: Same as adult

Contraindications: Avoid use with soft contact lenses.

Precautions: Skilled tasks Transient blurring of vision, warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for several hours.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Common: Temporarily stains skin, urine, tears and nasal secretions yellow, may permanently stain soft contact lenses and clothing.

Interactions: There are no known interactions where it is recommended to avoid concomitant use.

Tropicamide + Phenylephrine

Tropicamide ATC code: S01FA06

Phenylephrine ATC code: R01BA53

Eye drops, 0.8% + 5% w/v, LOU 4

Indications and dose

Adult

Diagnostic (Retinal photography, refractive errors, fundus examination/photography, slit lamp examination), Pre-operative (Dilate pupil to visualize structures behind the iris before surgical procedures, such as cataract extraction, vitrectomy, and retinal detachment surgery): Apply 1 drop of ophthalmic solution to the eye(s) every 3 to 5 minutes to conjunctival fornix as required up to a maximum of 3 drops. If necessary, this dose may be repeated once only, at least one hour after the first drop; Instillation should be done 15–30 minutes prior to the ophthalmic procedure.

Paediatric:

To dilate the pupil: a commercially available preparation of tropicamide 0.8% + phenylephrine HCl 5% is diluted in 1:1 ratio with a tear substitute (methylcellulose). One drop of the resulting solution is instilled every 3 to 5 minutes to conjunctival fornix up to a maximum of 3 drops.

Contraindications: Glaucoma, adhesions between the iris and the lens.

Precautions: Hypermetropic (long-sighted) (may precipitate acute angle-closure glaucoma), darkly pigmented iris (more resistant to pupillary dilatation, exercise caution to avoid overdosage).

Skilled tasks: Transient blurring of vision, warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Hepatic impairment: No dose reduction necessary.

Renal impairment: No dose reduction necessary.

Adverse effects: Common: Intolerance to bright light (glare), stinging on instillation, blurred vision (especially near vision), transient intraocular pressure elevation (especially in pre-existing ocular hypertension), visual disturbance.

Persistent ocular irritation (mucus discharge, severe watering discharge, superficial punctate keratopathy and characteristically no itch, punctal stenosis with prolonged use (years), insomnia, drowsiness.

Rare: Systemic toxicity, e.g., dryness of skin and mouth, fever, facial flushing, tachycardia, irritability, disorientation, ataxia, visual hallucinations, incoherent speech, delirium, psychosis, seizures, hyperactivity.

Interactions: There are no known interactions where it is recommended to avoid concomitant use.

Notes:

- Neonates are at increased risk of systemic toxicity.
- To minimize systemic absorption, apply finger pressure on the lacrimal sac for 1–2 minutes following instillation of the ophthalmic solution.
- Avoid contact of bottle tip with skin or eye.

16.2. Radiocontrast Media

Amidotrizoate

ATC code: V08AA01

Solution (oral and rectal use), 370–420 mg iodine/mL (as sodium or meglumine salt) (100 mL), LOU 4

Indications and dose

Adult

Retrograde cystourethrography, bladder instillation: 2 5 to 300 mL, dose depends on patient's age and degree of bladder irritability; may use >300 mL if bladder capacity allows; results are best when bladder is filled with contrast agent

Paediatric: Same as adult

Hepatic Impairment: dose adjustment is not necessary.

Renal Impairment: dose adjustment is not necessary.

Pregnancy considerations: Crosses the placenta. Procedure contraindicated in pregnancy unless risk benefit analysis deems procedure necessary as advised by admitting medical specialist.

Adverse Reactions: **Frequency not defined**: anaphylactoid reactions.

Drug Interaction (*indicates serious): Aldesleukin: May enhance the potential for allergic or hypersensitivity reactions to Iodinated Contrast Agents.

*Sodium iodide: Iodinated contrast agents may diminish the therapeutic effect of Sodium iodide: Avoid concurrent use.

Note:

- Intended for bladder instillation only,
- Not for intravascular or IV administration.
- Safe and effective use depends on proper dosage, correct technique, adequate precautions, and preparation for potential emergencies.
- Use sterile technique for administration.
- Avoid excessive pressure, rapid or acute bladder distention, and trauma

Barium Sulphate

ATC code: V08BA01

Aqueous suspension, 95% w/w concentration, 1 L, LOU 4

Paste (for oral or rectal use): 92% w/w concentration, LOU 4

Indications and dose

Adult

Radiographic examination of GIT: Route and dosage depend on procedure and preparation used (consult manufacturer's literature and/or specialist physician/radiographer).

Paediatric: Same as adult

Contraindications: Intestinal obstruction, intestinal perforation.

Precautions: Conditions which predispose to intestinal obstruction such as pyloric stenosis or lesions, conditions with risk of perforation such as acute ulcerative colitis, diverticulitis, or after rectal or colonic biopsy, sigmoidoscopy or radiotherapy, hereditary fructose intolerance (some preparations may contain fructose).

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Constipation or diarrhoea.

Rare GI obstruction, appendicitis, abdominal cramps and bleeding, perforation of bowel resulting in peritonitis, adhesions, granulomas, electrocardiographic changes with rectal administration, pneumonitis or granuloma formation may occur following accidental aspiration into lungs.

Interactions with other medicines:

There are no known interactions where it is recommended to avoid concomitant use.

Notes:

- Ensure adequate hydration after procedure to prevent severe constipation.
- Monitor electrolytes as some preparations contain sodium and potassium.

Iso-Osmolar Contrast Media

ATC code: V08AB

Solution for IV injection/infusion, 320 mg iodine/mL, 100 mL LOU 4

Indications and dose

Adult

Diagnostic radiography: Dosage of up to 1 mL/kg, exact dosage to be determined depending on the type of examination, age, weight, cardiac output, and general condition of the patient and the technique used. Adequate hydration should be ensured before and after administration as for other contrast media.

Paediatric

1 mL/kg to 3 mL/kg depending on the type of examination, age, weight, cardiac output, and general condition of the patient and the technique used. Adequate hydration should be ensured before and after administration as for other contrast media.

Hepatic impairment: Dose adjustment not necessary.

Renal impairment:

eGFR ≥30 mL/min/1.73 m2: Dose adjustment not necessary.

Risk for Nephrogenic systemic fibrosis development increases as renal function decreases.

eGFR <30 mL/min/1.73 m2: Use is contraindicated

Hemodialysis: If administered to patients already receiving hemodialysis, consider prompt hemodialysis following exposure (e.g., within 3 hours)

Adverse Effects: Common: Headache, Nausea, injection Site Reactions, Vasodilatation, Vomiting, Back pain, Urinary urgency, Chest pain, Pain, Dysgeusia, Abnormal vision.

Rare: Cardiac arrhythmia, cerebrovascular accident, ischemic heart disease, Cerebral edema (children), Diabetes insipidus (children), Mucous membrane disease (swelling, children), Fixed drug eruption (children), joint effusion (children), muscle cramps (children), Conjunctivitis (children), Acute renal failure, Aspiration, cyanosis, epistaxis (children), respiratory insufficiency

Drug Interaction (*indicates serious):

Aldesleukin: May enhance the potential for allergic or hypersensitivity reactions to Iodinated Contrast Agents.

*Metformin: Iodinated Contrast Agents may enhance the adverse/toxic effect of metformin.

*Sodium iodide: Iodinated Contrast Agents may diminish the therapeutic effect of sodium iodide.

Non Ionic Low Osmolar Water-Soluble Iodinated Contrast Media

ATC code: Not assigned

Injection, 300 mg iodine/mL, 50 mL, and 100 mL, LOU 4

Injection, 350 mg iodine/mL, 50 mL, and 100 mL, LOU 4

Injection, 300 mg iodine/mL, 50 mL, and 100 mL (for intrathecal, oral, intracavitary, and IV use), LOU 4

Injection, 350 mg iodine/mL, 50 mL, and 100 mL (for oral, intracavitary, and IV use), LOU 4

Indications and dose

Adult

Diagnostic radiography: Dosage varies depending on the type of examination, age, weight, cardiac output, and general condition of the patient and the technique used. Adequate hydration should be ensured before and after administration as for other contrast media.

Paediatric: Same as adult

Hepatic impairment: Dose adjustment not necessary.

Renal impairment:

eGFR ≥30 mL/min/1.73 m2: Dose adjustment not necessary. Risk for Nephrogenic systemic fibrosis development increases as renal function decreases.

eGFR <30 mL/min/1.73 m2: Use is contraindicated

Hemodialysis: If administered to patients already receiving hemodialysis, consider prompt hemodialysis following exposure (e.g., within 3 hours)

Adverse Effects: Common: Headache, Nausea, injection Site Reactions, Vasodilatation, Vomiting, Back pain, Urinary urgency, Chest pain, Pain, Dysgeusia, Abnormal vision.

Rare: Cardiac arrhythmia, cerebrovascular accident, ischemic heart disease, Cerebral edema (children), Diabetes insipidus (children), Mucous membrane disease (swelling, children), Fixed drug eruption (children), joint effusion (children), muscle cramps (children), Conjunctivitis (children), Acute renal failure, Aspiration, cyanosis, epistaxis (children), respiratory insufficiency

Drug Interaction (*indicates serious):

Aldesleukin: May enhance the potential for allergic or hypersensitivity reactions to Iodinated Contrast Agents.

*Metformin: Iodinated Contrast Agents may enhance the adverse/toxic effect of metformin.

*Sodium Iodide: Iodinated Contrast Agents may diminish the therapeutic effect of Sodium Iodide.

Note:

» Extravasation management: If extravasation occurs, stop infusion immediately and disconnect, remove needle/cannula, elevate extremity. Aspiration of extravasated contrast media is not recommended.

16.3. Magnetic Resonance Imaging Contrast Media

Gadobutrol

ATC code: V08CA09

Injection solution (IV), 1 mmol/mL, 7.5 mL and 15 mL, LOU 4

Indications and dose

Adult

Breast malignancy imaging, CNS imaging, and supra-aortic or renal artery angiography, IV: 0.1 mmol/kg (0.1 mL/kg); may begin imaging immediately after administration

Cardiac imaging, IV: 0.05 mmol/kg (0.05 mL/kg) at peak pharmacological stress, followed by 0.05 mmol/kg (0.05 mL/kg) at rest

Paediatric

CNS imaging, supraaortic or renal artery angiography

Neonates, children, and adolescents: Same as adult

Contraindications: Severe hypersensitivity reactions to gadobutrol or any component of the formulation.

Hepatic Impairment: Dose adjustment not necessary

Renal Impairment:

eGFR ≥30 mL/min/1.73 m2: Dose adjustment not necessary. Risk for Nephrogenic systemic fibrosis development increases as renal function decreases.

eGFR <30 mL/min/1.73 m2: Use is contraindicated

Hemodialysis: If administered to patients already receiving hemodialysis, consider prompt hemodialysis following exposure (e.g., within 3 hours)

Pregnancy: Gadolinium-based contrast agents may cross the placenta

Breastfeeding: Gadolinium-based contrast agents may be present in breast milk

Adverse Effects: Common: Headache, Nausea

Rare: Altered sense of smell, anaphylactic shock, anaphylaxis, angioedema, dizziness, dysgeusia, dyspnea, erythema of skin, feeling hot, hypersensitivity reaction, injection site reaction, loss of consciousness, maculopapular rash, malaise, nephrogenic systemic fibrosis, palpitations, paresthesia, parosmia, pruritus, seizure, sensation of cold, skin rash, tachycardia, urticaria, vomiting, xerostomia.

Interactions with other medicines: There are no known significant interactions.

Note:

» Extravasation management: If extravasation occurs, stop infusion immediately and disconnect, remove needle/cannula, elevate extremity. Aspiration of extravasated contrast media is not recommended.

Gadodiamide

ATC CODE: V08CA03

Solution for injection (IV), 0.5 mmol/mL, 20 mL, LOU 4

Indications and dose

Adult

Body imaging, kidney, IV: 0.05 mmol/kg (0.1 mL/kg)

Intrathoracic (noncardiac), intra-abdominal, pelvic cavities, IV: 0.1 mmol/kg (0.2 mL/kg)

CNS imaging, IV: 0.1 mmol/kg (0.2 mL/kg)

Magnetic resonance angiography (unlabeled use), IV: 0.1 mmol/kg (0.2 mL/kg)

Musculoskeletal imaging (off-label), IV: 0.3 mmol/kg (0.6 mL/kg)

Paediatric

Body imaging, IV

Child ≥2 years and adolescents, IV: Refer to adult dosing.

CNS imaging, IV

Children ≥2 years and adolescents ≤16 years: 0.1 mmol/kg (0.2 mL/kg)

Musculoskeletal imaging (off-label), IV

Adolescents ≥13 years: Refer to adult dosing.

Contraindications: Severe CKD (eGFR <30 mL/min/1.73 m2), acute kidney injury, hypersensitivity to gadodiamide or any component of the formulation

Hepatic Impairment: Dose adjustment not necessary.

Renal Impairment:

eGFR ≥30 mL/min/1.73 m2: Dose adjustment not necessary. Risk for NSF development increases as renal function decreases.

eGFR <30 mL/min/1.73 m2: Use is contraindicated

Hemodialysis: If administered to patients already receiving hemodialysis, consider prompt hemodialysis following exposure (e.g., within 3 hours)

Adverse Events: Common: Dizziness, headache, Nausea

Rare: Abdominal pain, acute exacerbations of multiple sclerosis, acute renal failure, ageusia, anaphylactoid shock, arthralgia, asthenia, ataxia, cardiac arrhythmia, cardiac failure, chest pain, decreased serum iron (asymptomatic, transitory), diaphoresis, diarrhea, dysgeusia, dyspnea, eructation, erythematous rash, fatigue, fever, flushing, hepatic insufficiency, increased serum creatinine, increased serum iron (asymptomatic, transitory), injection site reaction, malaise, melena, migraine, myalgia, MI, nephrogenic systemic fibrosis, pain, paresthesia, pruritus, renal insufficiency, rhinitis, rigors, seizure, skin changes (plaques), skin rash, syncope, thrombophlebitis, tinnitus, tremor, urticaria, vasodilation, visual disturbance, vomiting, xerostomia

Interactions with other medicines: There are no known significant interactions.

Gadopentate Dimeglumine

ATC code: V08ca01

Solution for injection (IV), 0.5 mmol/mL, 10 mL and 15 mL, LOU 4

Indications and dose

Adult

CNS imaging, IV: 0.1 mmol/kg (0.2 mL/kg)

Renal and aorto-ilio-femoral vasculature imaging, IV: 0.1 mmol/kg (0.2 mL/kg); calculate scan delay with test bolus (1 to 2 mL) or with automatic detection technique

Paediatric

CNS magnetic resonance imaging, IV

Infant and child <2 years: 0.1 to 0.2 mL/kg (0.05 to 0.1 mmol/kg); may begin imaging immediately after administration

Child ≥2 years and adolescent: 0.2 mL/kg (0.1 mmol/kg); may begin imaging immediately after administration

Hepatic Impairment: Dose adjustment not necessary.

Renal Impairment:

eGFR ≥30 mL/min/1.73 m2: Dose adjustment not necessary. Risk for Nephrogenic systemic fibrosis development increases as renal function decreases.

eGFR <30 mL/min/1.73 m2: Use is contraindicated

Hemodialysis: If administered to patients already receiving hemodialysis, consider prompt hemodialysis following exposure (e.g., within 3 hours)

Interaction with other medicines (*indicates serious):

Amisulpride (Oral): May enhance the QTc-prolonging effect of QT-prolonging Agents (Moderate Risk).

Chloroquine: QT-prolonging Miscellaneous Agents (Moderate Risk) may enhance the QTc-prolonging effect of Chloroquine.

Clofazimine: QT-prolonging Miscellaneous Agents (Moderate Risk) may enhance the QTc-prolonging effect of Clofazimine.

*Domperidone: QT-prolonging Agents (Moderate Risk) may enhance the QTc-prolonging effect of Domperidone. Management: Consider alternatives to this drug combination.

*Fexinidazole [INT]: May enhance the QTc-prolonging effect of QT-prolonging Agents (Moderate Risk). *Avoid combination*

Haloperidol: QT-prolonging Miscellaneous Agents (Moderate Risk) may enhance the QTc-prolonging effect of Haloperidol.

Ondansetron: QT-prolonging Miscellaneous Agents (Moderate Risk) may enhance the QTc-prolonging effect of Ondansetron.

Pentamidine (Systemic): QT-prolonging Miscellaneous Agents (Moderate Risk) may enhance the QTc-prolonging effect of Pentamidine (Systemic).

*Pimozide: May enhance the QTc-prolonging effect of QT-prolonging Agents (Moderate Risk). Avoid combination

QT-prolonging Antidepressants (Moderate Risk): May enhance the QTc-prolonging effect of Gadopentate dimeglumine

QT-prolonging Antipsychotics (Moderate Risk): Gadopentate dimeglumine may enhance the QTc-prolonging effect of QT-prolonging Antipsychotics (Moderate Risk).

QT-prolonging Class IC Antiarrhythmics (Moderate Risk): Gadopentate dimeglumine may enhance the QTc-prolonging effect of QT-prolonging Class IC Antiarrhythmics (Moderate Risk).

QT-prolonging Moderate CYP3A4 Inhibitors (Moderate Risk): May enhance the QTc-prolonging effect of Gadopentate dimeglumine

QT-prolonging Quinolone Antibiotics (Moderate Risk): May enhance the QTc-prolonging effect of QT-prolonging Quinolone Antibiotics

*QT-prolonging Strong CYP3A4 Inhibitors (Moderate Risk): May enhance the QTc-prolonging effect of Gadopentate dimeglumine. *Avoid combination*

Note:

» Significant Interactions with other medicines exist, requiring dose/frequency adjustment or avoidance.

17. Disinfectants & Antiseptics

17.1. Antiseptics

Chlorhexidine

ATC code: D08AC02

Solution, 5% (gluconate/digluconate) for dilution, LOU 2

Indications and dose

Adult

Antiseptic (pre-operative skin disinfection and hand hygiene), topical: 0.5% solution in ethanol (70%) or 2 or 4% detergent solution

Antiseptic (wounds, burns and other skin damage), topical: Apply 0.05% aqueous solution

Paediatric: Same as adult

Contraindications: Hypersensitivity

Precautions: Aqueous solutions are susceptible to microbial contamination, use sterilized preparation or freshly prepared solution and avoid contamination during storage or dilution, instruments with cemented glass components (avoid preparations containing surface active agents), irritant (avoid contact with middle ear, eyes, brain and meninges), not for use in body cavities, alcoholic solutions not suitable before diathermy, syringes and needles treated with chlorhexidine (rinse thoroughly with sterile water or saline before use), inactivated by cork (use glass, plastic or rubber closures), ethanol-based solutions are flammable.

Renal, hepatic impairment, pregnancy and breastfeeding: No dose adjustments

Adverse effects: Skin sensitivity and irritation, Corneal damage due to contact, hypersensitivity reactions

Interactions: Inactivated by soaps and other anionic materials. Activity may be reduced in the presence of suspending agents, insoluble powders or compounds. Insoluble salts may form in hard water. Chlorhexidine is inactivated by cork.

Notes:

- Most active against Gram-positive bacteria, with some Gram-negative activity. Spores and hydrophilic viruses are resistant. Chlorhexidine gluconate may be mixed with quaternary ammonium compounds for broader antimicrobial activity.
- **Disinfection of clean instruments:**
- Immerse for at least 30 minutes in 0.05% solution. The addition of 0.1% sodium nitrate minimizes metal corrosion.
- Emergency disinfection of clean instruments:
- Immerse for 2 minutes in 0.5% solution in ethanol (70%).

Ethanol (Alcohol)

ATC code: D08AX08

Solution, 70% (denatured), LOU 2

Indications and dose

Adult

Disinfection of skin prior to injection, venipuncture, or surgical procedures, topical: Apply 70% solution

Paediatric: Same as adult

Contraindications: None

Precautions: Avoid broken skin, when used as a surgical skin prep, avoid pooling under patient and allow to dry before using diathermy.

Hepatic impairment, renal, pregnancy and breastfeeding: No dose adjustments

Adverse effects: Skin dryness and irritation with frequent application. Absolute (undiluted) ethanol will produce greater skin irritation.

Interactions: No known significant clinical interactions.

Notes:

- Ethanol is a flammable liquid and should be kept cool and away from any heat source.
- Alternative alcohol products such as isopropanol are also effective agents. Ethanol alone is a short-acting antimicrobial agent. May be used in combination with other active agents such as 0.5% chlorhexidine or iodine. Ethanol is less effective on non-enveloped viruses (such as hepatitis A virus) and is not effective on fungal or bacterial spores.
- Do not use absolute ethanol as it is a less effective antimicrobial agent. Allow to dry completely for maximum effectiveness.

Povidone Iodine

ATC code: D08AG02

Solution, 10% (equivalent to iodine 1%), LOU 2

Indications and administration

Adult

Pre- and post-operative skin disinfection, topical: Apply undiluted

Antiseptic for minor wounds and burns, topical: Apply undiluted twice daily

Paediatric: Same as adult

Contraindications: Avoid regular or prolonged use in patients with thyroid disorders, those taking lithium, neonates and avoid in very low birth weight infants due to iodine absorption.

Precautions: Broken skin or to severe burns (see below), renal impairment, Large open wounds. The application of povidone iodine to large wounds or severe burns may produce systemic adverse effects such as metabolic acidosis, hypernatraemia and impairment of renal function.

Hepatic impairment: Avoid in severe hepatic impairment.

Renal impairment: Severe: avoid regular application to inflamed or broken mucosa.

Pregnancy: Second and third trimesters: sufficient iodine may be absorbed to affect the foetal thyroid.

Breastfeeding: Avoid

Adverse effects: Irritation of skin and mucous

membranes. May interfere with thyroid function tests, systemic effects (see under Precautions), hypersensitivity reactions.

Interactions: No known significant clinical interactions.

Notes:

- Povidone iodine solutions (i.e. surgical scrub, skin cleanser) should not be warmed or heated before use unless specific manufacturer labeling states otherwise. Upon heating, iodine can interact with dissolved oxygen causing a decrease in iodine concentration, or water evaporation may occur resulting in an increase in iodine concentration.
- Inactivated by organic material. Povidone iodine has broad antimicrobial activity, including against spores and viruses.

17.2. Disinfectants

Alcohol-Based Hand Rub

ATC code: V03AZ01

Solution, isopropyl alcohol 75%, LOU 1

Indications and dose

Adult

General hand and skin disinfection: Put enough sanitizer on hands to cover all surfaces and rub hands together until they feel dry.

Paediatric: Same as adult

Precautions: Avoid broken skin.

Hepatic impairment, renal, pregnancy and breastfeeding: No dose adjustments

Adverse effects: Skin dryness and irritation with frequent application.

Notes:

- Isopropyl alcohol is a flammable liquid and should be kept cool and away from any heat source.
- Use when soap and water are not available.

Glutaraldehyde (Glutaral)

ATC code: V07AV

Solution, 2%, LOU 2

Disinfection of clean instruments

- Completely immerse in undiluted 2% solution for 20 minutes at 20 °C. Up to 3 hours may be required for certain instruments (e.g., bronchoscopes with possible mycobacterial contamination). Rinse with sterile water or ethanol after disinfection and allow to dry completely.
- For endoscopes, ensure that all channels are clean. Immersion in undiluted 2% solution for 20 minutes at 20 °C will provide high-level disinfection.

Sterilization of clean instruments: Immerse in undiluted solution for up to 10 hours; rinse with sterile water or ethanol.

Contraindications: None

Precautions: Minimize occupational exposure. Handle with gloves, aprons and safety glasses in an area with adequate ventilation to avoid inhalation of vapour.

Hepatic impairment, renal, pregnancy and breastfeeding: No dose adjustments

Adverse effects: Skin sensitizer and toxic if inhaled or has direct contact with skin, eyes or mucous membranes. May cause nausea, headache, airway obstruction, asthma, rhinitis, eye irritation and dermatitis and skin discoloration.

Risk of occupational exposure to glutaral vapour may be higher in warm climates.

Interactions: no known clinical interactions.

Notes:

- Store below 15 °C. Protect from light.
- Thorough rinsing of endoscopes is required to prevent mucous membrane irritation and colitis.
- Ortho-phthalaldehyde may be used as an alternative agent with lower toxicity.

Sodium Hypochlorite

ATC code: D08AX07

Solution, 4–6% chlorine, LOU 1

Surface disinfection (minor contamination)

- Apply solutions containing 500–1000 ppm (0.05–0.1%) to clean surfaces.
- Apply solutions containing 5000 ppm (0.5%) for blood spills.

Instrument disinfection

- Soak in solution containing 1000 ppm (0.1%) for a minimum of 15 minutes.
- To avoid corrosion, do not soak for more than 30 minutes; rinse with sterile water.

Contraindications: Avoid exposure of product to flame.

Precautions: Hypochlorite solutions may delay wound healing.

Hepatic impairment, renal, pregnancy and breastfeeding: No dose adjustments

Adverse effects: Irritation and burning sensation on skin.

Interactions: The antimicrobial activity of chlorine base compounds is rapidly reduced in the presence of organic material, it is also pH dependent. Avoid mixing with solutions of strong acids or ammonia, the subsequent reactions can release toxic gases.

Notes:

- Broad-spectrum antimicrobial with sporicidal activity (at optimum pH 7.6). Corrosive to metals with repeated application. Deteriorates with exposure to light and heat. Shelf life of diluted ingredients < 7 days.
- Spillage on skin or eyes should be washed with copious amounts of water.

18. Diuretics

Amiloride

ATC code: C03DB01

Tablet, 5 mg (as HCl), LOU 4

Indications and dose

Adult

Oedema (monotherapy), oral: Initially 10 mg daily or initially 5 mg twice daily, adjusted according to response; maximum 20 mg per day

Potassium conservation when used as an adjunct to thiazide or loop diuretics for hypertension or congestive heart failure, oral: Initially 5 mg daily, increasing to 10 mg daily if necessary; maximum, 20 mg daily

Potassium conservation when used as an adjunct to thiazide or loop diuretics for hepatic cirrhosis with ascites, oral: Initially 5 mg daily

Paediatric

Adjunct to thiazide or loop diuretics for oedema in heart failure and hepatic disease (where potassium conservation is desirable), oral

Neonate: 0.1 to 0.2 mg/kg twice daily

Child 1 month to 11 years: 0.1 to 0.2 mg/kg twice daily, maximum 20 mg/day

Child 12 to 17 years: 5 to 10 mg twice daily

Contraindications: Hypersensitivity to amiloride, Hyperkalemia, severe renal failure, Concomitant use with potassium sparing diuretic, or potassium supplementation, Impaired renal function

Precautions: Monitor electrolytes, particularly potassium, diabetes mellitus, the elderly (reduce dose)

Hepatic Impairment: Dose adjustment necessary. Use with caution.

Renal Impairment:

Administer at 50% of normal dose for CrCl 10 to 50 mL/min.

Do not use if CrCl <10 mL/min.

Avoid use in older adults ≥65 years of age with a CrCl <30 mL/min due to the risk of hyperkalemia and hyponatremia.

Pregnancy: Not to be used to treat gestational hypertension.

Breastfeeding: Avoid, no information available.

Adverse Effects: Common: Dizziness, fatigue, headache, hyperkalemia, dehydration, gynecomastia, hyperchloremic metabolic acidosis, hyponatremia, abdominal pain, change in appetite, constipation, diarrhea, gas pain, nausea, vomiting, impotence, muscle cramps, weakness, cough, dyspnea

Rare: Alopecia, bladder spasm, cardiac arrhythmia, chest pain, dysuria, GI hemorrhage, increased intraocular pressure, jaundice, orthostatic hypotension, palpitations, polyuria

Interaction with other medicines (*indicates serious):

Alfuzosin, Amphetamines, Angiotensin II Receptor Blockers, ACEIs, Antipsychotic Agents (Second Generation [Atypical]), Barbiturates, Digoxin, *Cyclosporine, Duloxetine, *Eplerenone, Heparin, Levodopa-Containing, Products, Methylphenidate, Nitroprusside

Nonsteroidal Anti-Inflammatory Agents, Opioid Agonists, Phosphodiesterase 5 Inhibitors, *Potassium Salts, Quinidine, *Spironolactone, Tacrolimus, Tolvaptan

Furosemide (Frusemide)

ATC code: C03CA01

Injection, 10 mg/mL in 2-mL amp, LOU 4

Oral liquid, 20 mg/5 mL, LOU 4

Tablet, 40 mg, LOU 4

Indications and dose

Adult

Oedema, oral: Initially 40 mg daily, preferably in the morning; usual maintenance dose, 20–40 mg daily; may be increased to 80 mg daily or more in resistant oedema

Acute pulmonary oedema, slow IV: 20–50 mg, increased incrementally in 20-mg steps every 2 hours, if necessary; if the effective single dose is more than 50 mg, consider using slow IV infusion at a rate not exceeding 4 mg/min,

Oliguria (glomerular filtration rate <20 mL/min), slow IV (rate not exceeding 4 mg/min): Initially 250 mg over 1 hour; if urine output is not satisfactory, during the hour after the first dose, infuse 500 mg over 2 hours then, if there is no satisfactory response during the hour after the second dose, infuse 1 g over 4 hours; if there is no response after the third dose, dialysis is probably necessary; effective dose (up to 1 g) can be repeated every 24 hours

Paediatric

Oedema in heart failure, renal disease and hepatic disease; Pulmonary Oedema, oral:

Neonate: 0.5 to 2 mg/kg every 12 to 24 hours (every 24 hours if corrected gestational age under 31 weeks)

Child 1 month to 11 years: 0.5 to 2 mg/kg 2 to 3 times daily; higher doses may be required in resistant oedema; maximum 12 mg/kg per day.

Child 12 to 17 years:20 to 40 mg daily increased to 80 to 120mg daily in resistant oedema.

Oedema in heart failure, renal disease and hepatic disease; Pulmonary Oedema, Slow IV:

Neonate: 0.5 to 1 mg/kg every 12 to 24 hours (every 24 hours if corrected gestational age under 31 weeks)

Child 1 month to 11 years: 0.5 to 1 mg/kg every 8 hours (maximum per dose 40mg every 8 hours) as required; maximum 6mg/kg per day.

Child 12 to 17 years: 20 to 40 mg every 8 hours as required, higher doses may be required in resistant oedema.

Oedema in heart failure, renal disease and hepatic disease; Pulmonary Oedema, Continuous IV infusion:

Child, all ages: 0.1 to 2mg/kg/hour

Oedema in heart failure, renal disease and hepatic disease; Pulmonary Oedema following cardiac surgery, Continuous IV infusion:

Child, all ages: Initially 100micrograms/kg/hour, dose doubled every two hours until urine output exceeds 1ml/kg/hour.

Oliguria, oral:

Child 12 to 17 years: Initially 250mg daily, then increased in steps of 250mg every 4 to 6 hours (maximum per dose 2g) if required

Oliguria, IV infusion

Child 1 month to 11 years: 2 to 5 mg/kg up to four times daily; Maximum 1gm per day

Child 12 to 17 years: Initially 250mg, dose to be administered over 1 hour, increased to 500mg which is given if satisfactory urine output is not obtained; dose is administered over two hours then increased to 1g which is given if satisfactory response is not obtained within the subsequent hour; the dose is administered over 4 hours. If no response is obtained, dialysis may be required; effective dose up to 1g given at a maximum rate of 4mg/minute can be repeated every 24hours.

Contraindications, Precautions, use in hepatic and renal impairment, pregnancy and breastfeeding adverse effects, interactions with other medicines: *See Furosemide in section 14.4, medicines used in heart failure*

Notes:

- Advise patient or caregiver that if taking furosemide twice daily, take the first dose in the morning and the second dose before 18:00 to prevent overnight diuresis.
- Monitor potassium during therapy. Consider the addition of potassium-sparing diuretics or potassium supplements.
- To avoid ototoxicity, IV doses should be given no faster than 0.5 mg/kg per minute (doses < 120 mg) or 4 mg/min (doses ≥ 120 mg)

Hydrochlorothiazide

ATC code: C03AA03

Tablet (scored), 25 mg, LOU 4

Indications and dose

Adult

Oedema, oral: Initially 25 mg daily on rising, increased to 50 mg daily if necessary

Elderly: Initially 12.5 mg daily on rising

Severe oedema in patients unable to tolerate loop diuretics, oral: Up to 100 mg either daily or on alternate days; maximum 100 mg daily

Nephrogenic diabetes insipidus, oral: Initially up to 100 mg daily

Paediatric

Oedema, oral

Infant under 6 months: 2 to 3.3 mg/kg daily in two divided doses; maximum dose 37.5 mg daily

Child over 6 months: 2 mg/kg daily in two divided doses; maximum dose 200 mg daily

Contraindications, Precautions, use in hepatic and renal impairment, pregnancy and breastfeeding, adverse effects and interactions with other medicines:

See Hydrochlorothiazide in section 14.3.5, Thiazide and Thiazide like diuretics

Mannitol

ATC code: B05BC01

Injectable solution, 20%, LOU 4

Indications and dose

Adult

Assessment of renal function, test dose (if patient is oliguric or if renal function is inadequate), by IV infusion: As a 20% solution infused over 3–5 minutes, 200 mg/kg; repeat test dose if urine output is <30–50 mL/hour; if response is inadequate after a second test dose, re-evaluate the patient

Cerebral oedema, by IV infusion: As a 20% solution infused rapidly, 1 g/kg to be administered over 30–60 min; may be repeated after 4–8 hours

Raised intraocular or intracranial pressure (emergency treatment or before surgery), by IV infusion: As a 20% solution infused over 30–60 minutes, 0.25–2 g/kg

Paediatric

Assessment of renal function, test dose (to assess adequate renal function), by IV infusion

Child all ages: 200 mg/kg (maximum dose 12.5 g) given over 3 to 5 minutes to produce urine flow of at least 1 mL/kg/hour for 1–3 hours

Cerebral oedema, raised intraocular pressure, by IV infusion

Infant or child 1 month to 12 years: 0.25–1.5 g/kg given over 30 to 60 minutes, repeated if necessary 1 to 2 times after 4 to 8 hours

Contraindications: Pulmonary oedema, intracranial bleeding (except during craniotomy), severe congestive heart failure, metabolic oedema with abnormal capillary fragility, severe dehydration, renal failure (unless test dose produces diuresis).

Precautions: Monitor fluid and electrolyte balance, monitor renal function.

Hepatic impairment: Dose reduction not required.

Renal impairment: All degrees of impairment: avoid unless test dose produces a diuretic response.

Pregnancy and breastfeeding: Avoid

Adverse effects: Fluid and electrolyte imbalance, circulatory overload, acidosis. Dry mouth, thirst, nausea, vomiting, oedema, raised intracranial pressure, arrhythmia, hypotension, pulmonary oedema, chest pain, headache, seizures, dizziness, chills, fever,

pulmonary oedema (particularly in diminished cardiac reserve), chest pain, visual disturbances, hypotension or hypertension, urticaria, hypersensitivity reactions, extravasation may cause oedema, skin necrosis, thrombophlebitis. Acute renal failure (large doses), congestive heart failure.

Interactions with other medicines (*indicates serious):

There are no known interactions where it is recommended to avoid concomitant use.

Notes:

» Solutions containing more than mannitol 15% may crystallize during storage, crystals must be redissolved by warming solution before use and solution must not be used if any crystals remain, IV administration sets must have a filter, mannitol should not be administered with whole blood or passed through the same transfusion set as blood.

Metolazone

See Metolazole Section 14.4

Spironolactone

ATC code: C03DA01

Tablet, 25 mg, LOU 4

Tablet, 100 mg, LOU 4

Indications and dose

Adult

Oedema, ascites in cirrhosis of the liver, oral: 100 to 400 mg daily, adjusted according to response

Malignant ascites, oral: Initially 100 to 200 mg daily, then increased, if necessary, to 400 mg daily; maintenance dose adjusted according to response

Nephrotic syndrome, oral: 100 to 200 mg daily

Oedema in congestive heart failure, oral: Initially 100 mg daily, alternatively initially 25–200 mg daily; dose may be taken as a single dose or divided doses; maintenance dose adjusted according to response

Paediatric

Diuresis in congestive heart failure, ascites, oedema and nephrotic syndrome, reduction of hypokalaemia induced by other diuretics or amphotericin, oral

Neonate: 1 to 2 mg/kg daily in 1 to 2 divided doses

Infant or **child 1 month to 12 years:** 1 to 3 mg/kg daily in 1 to 2 divided doses (maximum 100 mg daily)

Primary hyperaldosteronism, resistant ascites, oral

Neonate: Up to a maximum of 7 mg/kg daily may be used

Infant or **child 1 month to 12 years:** Up to a maximum of 9 mg/kg daily (total maximum 400 mg daily) may be used

Contraindications, Precautions, use in hepatic and renal impairment, pregnancy and breastfeeding, adverse effects and interactions with other medicines:

See Spironolactone in section 14.3.6.2, Potassium sparing diuretics

***indicates serious**

Notes:

» Advise patient and/or caregiver **not** to take potassium supplements while taking this medication.

Torsemide

ATC code: C03CA04

Tablet, 10 mg, 20mg, LOU 4

Indications and dose

Adult

Treatment of edema associated with heart failure or renal disease: 10-20 mg per day initially; may increase dose by doubling until desired diuretic effect is achieved.

Paediatric: No information is available.

Contraindications: Renal failure (anuria or renal dysfunction) hepatic coma, hypotension, hypersensitivity to torasemide and sulphonylureas, cardiac arrhythmias, concurrent administration with aminoglycosides or cephalosporins.

Precautions: Hypokalaemia, hyponatraemia, hypovolaemia . careful monitoring of patients with hyperuricemia/gout glucose intolerance. Long term use of torsemide regular monitoring of creatinine,lipids,glucose is required

Hepatic impairment: no dose adjustment required. Do not use in hepatic coma.

Renal impairment: no dose adjustment required.

Pregnancy: Should be avoided

Breastfeeding: Avoid use

Adverse effects: Excessive urination, Headache electrolyte imbalance, Dizziness, Rhinitis, Constipation

Interactions with other medicines (*indicates serious): Anti-arrhythmics: risk of cardiac toxicity with anti-arrhythmics

Antifungals: increased risk of hypokalaemia with amphotericin.

Antihypertensives: enhanced hypotensive effect

Antibacterials: increased risk of ototoxicity with aminoglycosides, polymyxins and vancomycin; avoid. concomitant use with lymecycline.

Antiepileptics: increased risk of hyponatraemia with carbamazepine.

19. Gastrointestinal Medicines

19.1. Antiulcer Medicines

Lansoprazole

ATC code: A02BC03

Tablet (dispersible), 15 mg, LOU 4

Indications and dose

Paediatric

Benign gastric ulcer, GERD, duodenal ulcer, prophylaxis and maintenance, NSAIM-associated duodenal ulcer and gastric ulcer, Acid-related dyspepsia, Fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis

Child 1 to 11 years, less than 30 kg: 15 mg orally once daily for up to 12 weeks; may increase to 30 mg twice daily if symptoms persist after 2 weeks

Child 1 to 11 years, more than 30 kg: 30 mg orally once daily for up to 12 weeks; may increase to 30 mg twice daily if symptoms persist after 2 weeks

Child 12 years or older: 30 mg orally once daily for up to 8 weeks

Contraindications: hypersensitivity to the components and ingredients, use of rilpivirine-containing products, apalutamide.

Hepatic impairment: Caution in mild and moderate impairment.

Severe impairment: 15 mg orally once daily.

Renal impairment: Dose reduction not necessary.

Discontinue use in acute tubulointerstitial nephritis.

Pregnancy: Use not recommended unless clearly needed. Manufacturer advises avoid

Breastfeeding: Avoid although amounts excreted in breastmilk are unlikely to be harmful to newborn infants.

Adverse effects: Common: dry throat, abdominal pain, cramps, bloating, constipation, diarrhoea, vomiting, mildly elevated AST/ALT, Drowsiness, Headaches, somnolence, dizziness, vertigo, visual disturbances

Rare: CV: hypertension, hypotension/ syncope, MI, cardiac arrhythmia, palpitations, Dermatologic: urticaria, pruritus, Hematologic: thrombocytopenia, leucopaenia, leukocytosis, anaemia, Endocrine: hyperglycaemia, hyperlipidaemia, Eosinophilia, Oedema, Fatigue

Interaction with other medicines: Clopidogrel: PPIs may diminish therapeutic effect of clopidogrel, Fluconazole: may increase the serum concentrations of PPIs (manage by monitoring therapy), Ferrous sulphate: the absorption of iron salts may be decreased because gastric acid secretion is inhibited by PPIs, Methotrexate: consider temporary withdrawal of lansoprazole concomitantly with high-dose methotrexate, Prolonged treatment (>2 years) may lead to malabsorption of dietary vitamin B12 thus deficiency.

Notes:

- Medicine used in paediatrics in situations where omeprazole is unsuitable
- Dosing time mainly in the morning, 30 minutes prior to breakfast
- Initial doses should start at the lowest dose according to body weight, age and severity of disease then titrated upwards to the tolerated effective therapeutic dose
- Lansoprazole should be taken at least an hour before taking sucralfate or other antacid medicines
- Therapeutic monitoring especially in long-term therapy: Magnesium levels, vitamin B12 levels, Bone fractures in patients at high risk for osteoporosis-related events
- consider tapering before discontinuing

Omeprazole

ATC code: A02BC01

Powder for injection, 40 mg (as sodium salt), LOU 4

Capsule, 20 mg, LOU 3

Indications and dose

Adult

GERD, oral: 20 mg once daily for 4–8 weeks

Severe esophagitis, oral: 40 mg once daily for at least 8 weeks; continue as maintenance treatment if appropriate

Helicobacter pylori eradication, oral: 20 mg or 40 mg twice daily as part of an appropriate combination regimen with antibiotics

Peptic ulcer disease, uncomplicated ulcer, oral: 20 to 40 mg once daily for 4–8 weeks

Complicated ulcer (perforation, penetration, or gastric outlet obstruction), oral: 40 mg twice daily for 4 weeks, followed by 40 mg once daily

Stress ulcer prophylaxis in select critically ill patients, oral or via NG tube: 40 mg once daily

Zollinger-Ellison syndrome, oral: 40 mg twice daily up to a maximum of 180 mg/day; once acid output has been controlled, maintenance dose of 10–180 mg

NSAIM-associated peptic ulcer, oral: 20 mg once daily for 4 weeks; continue for a further 4 weeks if not fully healed

Prophylaxis against NSAIM-associated peptic ulcer, oral: 20 mg once daily

Major peptic ulcer bleeding following endoscopic treatment, IV: Initially 80 mg, to be given over 40–60 minutes, then (by continuous IV infusion) 8 mg/hour for 72 hours; subsequent dose then changed to oral therapy

Treatment and prevention of benign peptic ulcers, NSAIM-associated ulcers, and GERD, IV: 40 mg once daily until oral administration possible

Paediatric

Helicobacter pylori eradication, used in combination with antibacterials, oral

Child 5–11 years: 1–2 mg/kg once daily, max daily dose 40 mg,

Child 12–17 years: 40 mg once daily

Gastric and duodenal ulcers

Child: 1–2 mg/kg (maximum 40 mg) once daily

GERD, stricturing oesophagitis, NSAIM-associated gastric and duodenal ulcers prophylaxis and treatment, Zollinger-Ellison syndrome, acid-related dyspepsia, fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis, oral

Child (body weight 10 to 19 kg): 1 mg/kg once or twice daily (maximum 40 mg/day).

Child (body weight 20 and above): 20 mg once daily, increased if necessary to 40 mg once daily

GERD, stricturing oesophagitis, NSAIM-associated gastric and duodenal ulcers prophylaxis and treatment, Zollinger-Ellison syndrome, acid-related dyspepsia, fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis, IV

Child 1 month–11 years: Initially 500 micrograms/kg once daily (max. per dose 20 mg), increase if necessary to 2 mg/kg once daily (max. per dose 40 mg), injection to be given over 5 minutes

Child 12–17 years: 40 mg once daily, injection to be given over 5 minutes

Hepatic impairment: No more than 700 micrograms/kg (maximum 20 mg) once daily.

Renal impairment: Dose reduction not necessary.

Pregnancy: Unknown harm

Breastfeeding: secreted in breastmilk, unknown harm

Adverse effects: Common: Headache, nausea, vomiting, diarrhoea, abdominal pain, constipation, flatulence. Rash, itch, dizziness, fatigue, drowsiness, insomnia, dry mouth, decreased absorption of cyanocobalamin (vitamin B12) with long-term use, paraesthesia.

Rare Gynaecomastia, myalgia, myopathy, arthralgia, blurred vision, taste disturbance, interstitial nephritis, peripheral oedema, raised liver enzymes, hepatitis, jaundice, thrombocytopenia, leukopenia, skin reactions (including SJS, toxic epidermal necrolysis, photosensitivity), hypersensitivity reactions, alopecia, confusion, haemolytic anaemia.

Interaction with other medicines (*indicates serious):

Ciclosporin: may increase levels and effect of ciclosporin.

*Methotrexate: may increase concentration and toxicity of methotrexate.

Phenytoin: may increase levels and effect of phenytoin.

Saquinavir: may increase concentration and toxicity of saquinavir.

*Tacrolimus: may increase concentration and toxicity of tacrolimus.

*Warfarin: may increase INR and anticoagulant effects.

Notes:

- Standard preparations: swallow tablet or capsule whole, do not crush or chew.
- Alternatively, some dispersible preparations are available and these may be dispersed in water, orange juice or yoghurt, take within 30 minutes of mixing.
- Where child cannot swallow capsule, lansoprazole dispersible tablet or alternative dispersible medication should be used.

Pantoprazole

ATC code : A02BC02

Dispersible tablet, 20mg, capsule 20mg, capsule 40mg, LOU 3

Powder for injection, 40mg, LOU 4

Indications and dose

Adult

Gastroesophageal Reflux Disease (GERD), Oral: 40mg once daily for 4-8weeks, IV injection 40mg once daily or by IV infusion until oral administration can be resumed, injection to be given over at least 2 minutes and infusion over at least 15 minutes.

Dyspepsia: Oral 20mg once daily for 4 weeks or 40mg once daily for 4 weeks if cause is unknown.

Uncomplicated gastric ulcer: Oral 40 mg daily for 8 weeks; increased if necessary up to 80 mg daily, dose increased in severe cases

Complicated (perforation, penetration or gastric outlet obstruction) gastric ulcer: IV 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

Duodenal ulcer: Oral 40 mg daily for 4 weeks; increased if necessary up to 80 mg daily, dose increased in severe cases. IV 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

NSAID-associated peptic ulcer disease: Oral 40 mg once daily for 8 weeks

Prophylaxis against NSAID-associated gastric or duodenal ulcer: Oral 20mg once daily

Severe oesophagitis: Oral 40 mg once daily for 8 weeks, continue as maintenance treatment if appropriate or IV 40mg once daily for 7-10days then resume oral administration.

Zollinger-Elison syndrome (and other hyper secretory syndromes): Oral 80 mg once daily initially (max. per dose 80 mg), adjusted according to response, up to 240mg/day. IV injection or infusion 80mg 2-3 times daily up to 7days or until patient is able to swallow.

H. pylori eradication: Oral 40 mg twice daily for 7 days as part of an appropriate combination regimen with antibiotics

Paediatrics

Children < 5years: Safety and efficacy not established

Children 5 years and older: *Short term treatment of erosive oesophagitis associated with GERD*: 15 to <40kg Oral 20mg once daily for up to 8 weeks

40kg or greater: Oral 40mg once daily for up to 8weeks

Contraindications: Hypersensitivity to the active ingredient or any of the excipients in the formulation.

Hepatic impairment: Adjust dose to a maximum of 20mg daily in severe liver impairment. Monitor liver function and discontinue if deterioration.

Renal impairment: Dose reduction may not be necessary.

Pregnancy: Avoid unless benefits outweigh the risks.

Breastfeeding: Small amounts secreted in breastmilk and not harmful.

Adverse effects: Sleep disturbances, headache and dizziness, fundic gland polyps, abdominal pain, diarrhoea, nausea and vomiting, increased liver enzymes, rash, pruritus, angioedema, bone fractures.

Drug interactions (*serious)

*Protease inhibitors e.g. atazanavir, ritonavir- reduces bioavalability

*Medicines with a pH-dependent pharmacokinetics e.g. azole antifungals (fluconazole, Ketoconazole)- reduces bioavailabilty

*Methotrexate – increases amount and toxicity

Warfarin

Notes

- Standard preparations: swallow tablet or capsule whole, do not crush or chew.
- Dispersible preparations may be dispersed in water, orange juice or yoghurt, take within 30 minutes of mixing.
- Directions for administration: for IV infusion, give intermittently in dextrose 5% or normal saline; reconstitute 40mg with 10mL normal saline and dilute with 100mL of infusion fluid; give 40 mg over 15 minutes.

19.2. Antiemetics

Dexamethasone

ATC code: H02AB02

Tablet, 0.5 mg, 2 mg, 4 mg, LOU, 4

Injection, 4mg/ml, LOU 4

Indications and dose

Adult

Nausea and vomiting induced by single-day IV chemotherapy regimen

Highly emetogenic chemotherapy, oral

- Day of chemotherapy: 12 mg administered prior to chemotherapy in combination with other antiemetics
- Post-chemotherapy days: 8 mg once or twice daily on days 2 to 4.

Moderately emetogenic chemotherapy, oral

- Day of chemotherapy: 8–12 mg in combination with other antiemetics
- Post-chemotherapy days: 8 mg on days 2 and 3

Low emetogenic chemotherapy, oral

- 4 to 8 mg administered as a single agent

Paediatric

Chemotherapy-induced nausea and vomiting, oral

Child all ages: 0.2 mg/kg (maximum 8 mg) then 0.1 mg/kg/dose (maximum 4 mg) every 6 hours, in conjunction with other antiemetics

Contraindications: Untreated systemic infection (unless condition is life threatening), administration of live virus vaccines.

Precautions: Increased susceptibility to and severity of infection, activation or exacerbation of TB, amoebiasis, strongyloidiasis, risk of severe chickenpox in non-immune patients (varicella zoster immunoglobulin required if exposed to chickenpox), avoid exposure to measles (normal immunoglobulin possibly required if exposed), diabetes mellitus, peptic ulcer, hypertension, corneal perforation, osteoporosis, myasthenia gravis.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Incidence of adverse effects is related to dose and duration of treatment. Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.

Common: Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects (Psychiatric effects Include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium and psychosis are less common).

IV - Transient itching, burning or tingling in perineal area (after IV bolus).

Rare: Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions including anaphylaxis.

Interaction with other medicines (*indicates serious):

Acetylsalicylic acid: increased risk of GI bleeding and ulceration, dexamethasone reduces plasma salicylate concentration.

Albendazole: plasma albendazole concentration possibly increased.

Amphotericin B: increased risk of hypokalaemia.

* Carbamazepine: accelerated metabolism of dexamethasone (reduced effect).

Contraceptives, oral: oral contraceptives containing estrogens increase plasma concentration of dexamethasone.

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of dexamethasone.

Furosemide: antagonism of diuretic effect, increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect, increased risk of hypokalaemia.

Ibuprofen: increased risk of GI bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

* Lopinavir: possibly reduced plasma lopinavir concentration.

Metformin: antagonism of hypoglycaemic effect.

* Methotrexate: increased risk of haematological toxicity.

Phenobarbital: metabolism of dexamethasone accelerated (reduced effect).

Phenytoin: metabolism of dexamethasone accelerated (reduced effect).

Praziquantel: plasma praziquantel concentration reduced.

Propranolol: antagonism of hypotensive effect.

Rifampicin: accelerated metabolism of dexamethasone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with dexamethasone.

Domperidone

ATC code: A03FA03

Oral liquid, 5 mg/mL, LOU 5

Tablet: 10 mg, LOU 3

Indications and dose

Adult

Relief of nausea and vomiting, oral: 35 kg and above, 10 mg up to 3 times a day for a maximum of 1 week (maximum 30 mg per day)

GI pain in palliative care, oral: 10 mg 3 times a day, before meals

Paediatric

Relief of nausea and vomiting, oral

Child <12 years (body weigh <35 kg): Not indicated

Child 12–17 years (body weight 35 kg and above): 10 mg up to 3 times a day for a usual maximum of 1 week, maximum 30 mg per day

Contraindications: Cardiac disease, conditions where cardiac conduction is, GI haemorrhage, GI mechanical obstruction, GI mechanical perforation, if increased GI motility harmful, prolactinoma

Precautions: Patients over 60 years—increased risk of ventricular arrhythmia (in adults)

Hepatic impairment: Avoid in moderate to severe impairment.

Renal impairment: Reduce frequency

Adverse effects: Common: Dry mouth, Anxiety, asthenia, breast abnormalities, diarrhoea, drowsiness, headache, breastfeeding disorders, libido loss, arrhythmias, depression, gynaecomastia, menstrual cycle irregularities, movement disorders, oculogyric crisis, QT interval prolongation, seizure, sudden cardiac death, urinary retention.

Interaction with other medicines (*indicates serious)

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors).

Fosfomycin: May decrease the serum concentration of Fosfomycin.

*Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates.

*Haloperidol: May enhance the QTc-prolonging effect of Domperidone.

Levosulpiride: May enhance the adverse/toxic effect of Levosulpiride.

*Ondansetron: Domperidone may enhance the QTc-prolonging effect of Ondansetron.

*Pentamidine (Systemic): Domperidone may enhance the QTc-prolonging effect of Pentamidine (Systemic).

Simeprevir: May increase the serum concentration of CYP3A4 Substrates

Sirolimus: May increase the serum concentration of Sirolimus.

Fosaprepitant

ATC code: A04AD12

Injection, 150 mg, LOU 5

Indications and dose

Adult

Prevention of chemotherapy-induced nausea and vomiting associated with moderate and highly emetogenic chemotherapy, IV: 150 mg given over 20–30 minutes and given 30 minutes before chemotherapy on day 1 of cycle only and given in combination with other antiemetics

Paediatric

Prevention of chemotherapy-induced nausea and vomiting associated with moderate and highly emetogenic chemotherapy, IV

Infants ≥6 months weighing ≥6 kg and child <2 years, 5 mg/kg once; maximum dose 150 mg/dose; administered over 60minutes and given 30 minutes before chemotherapy on day 1 of cycle only and given in combination with other antiemetics

Child 2 to <12 years, *single-day chemotherapy regimens:* 4 mg/kg once; maximum dose 150 mg/dose; administered over 60minutes and given 30 minutes before chemotherapy on day 1 of cycle only and given in combination with other antiemetics

Children ≥12 years and adolescents ≤17 years, *single-day chemotherapy regimens:* 150 mg once, administered over 30 minutes and given 30 minutes before chemotherapy on day 1 of cycle only and given in combination with other antiemetics

Contraindications: acute porphyrias, hypersensitivity to fosaprepitant or any component of the formulation, concurrent use with pimozide

Hepatic impairment: Use caution in moderate to severe impairment

Renal impairment: No dose adjustment necessary

Adverse effects: Common: Appetite decreased, asthenia, constipation, GI discomfort, headache,

hiccups, anaemia, anxiety, burping, dizziness, drowsiness, dry mouth, febrile neutropenia, flushing, GI disorders, malaise, nausea, palpitations, skin reactions, thrombophlebitis, urinary disorders, vomiting

Rare: cardiovascular disorder, chest discomfort, cognitive disorder, conjunctivitis, cough, disorientation, euphoric mood, gait abnormalities, hyperhidrosis, increased risk of infection, muscle spasms, muscle weakness, oedema, oropharyngeal pain, photosensitivity reaction, polydipsia, seborrhoea, SCARs, sneezing, stomatitis, taste altered, throat irritation, tinnitus, weight loss, dysarthria, dyspnoea, insomnia, miosis, sensation abnormal, visual acuity decreased, wheezing

Interaction with other medicines (*indicates serious)

Alprazolam: May increase the serum concentration of alprazolam.

*Astemizole: Fosaprepitant may increase the serum concentration of Astemizole.

Clofazimine: May increase the serum concentration of CYP3A4 Substrates.

*Corticosteroids (Systemic): Fosaprepitant may increase the serum concentration of Corticosteroids (Systemic).

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates.

Dofetilide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Dofetilide. *Monitor therapy*

*Estrogen Derivatives (Contraceptive): Fosaprepitant may decrease the serum concentration of Estrogen Derivatives (Contraceptive).

*Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates.

Ifosfamide: Fosaprepitant may increase the serum concentration of Ifosfamide. Specifically, concentrations of the toxic metabolites of ifosfamide may increase.

Midazolam: May increase the serum concentration of Midazolam.

Nimodipine: May increase the serum concentration of Nimodipine.

Paroxetine: May decrease serum concentrations of the active metabolite(s) Fosaprepitant.

*Pimozide: Fosaprepitant may increase the serum concentration of Pimozide. The active metabolite aprepitant is likely responsible for this effect. *Avoid combination*

*Progestins (Contraceptive): Fosaprepitant may decrease the serum concentration of Progestins (Contraceptive).

Simvastatin: May increase serum concentrations of the active metabolite(s) of Simvastatin.

Tacrolimus (Systemic): May increase the serum concentration of Tacrolimus

*Terfenadine: Fosaprepitant may increase the serum concentration of Terfenadine.

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates

Warfarin: Fosaprepitant may decrease the serum concentration of vitamin K Antagonists.

Notes:

- Adjunct to dexamethasone and a 5HT3-receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy.
- Effectiveness of hormonal contraceptives is reduced. Effective non-hormonal methods of contraception are necessary during treatment and for 2 months after stopping fosaprepitant.
- The KEML includes fosaprepitant and not aprepitant dosing included for the IV fosaprepitant only

Metoclopramide

ATC code: A03FA01

Injection, 5 mg (HCl)/mL in 2-mL amp, LOU 2

Tablet, 10 mg (HCl), LOU 2

Indications and dose

Adult

Symptomatic treatment of nausea and vomiting, including that associated with acute migraine, delayed chemotherapy-induced nausea and vomiting, radiotherapy-induced nausea and vomiting, prevention of post-operative nausea and vomiting, oral/IM injection/ slow IV injection

- Body weight up to 60 kg: Up to 500 micrograms/kg daily in 3 divided doses
- Body weight 60 kg and above: 10 mg up to 3 times a day

Hiccup in palliative care, oral/IM injection/SC injection: 10 mg every 6–8 hours

Nausea and vomiting in palliative care, oral: 10 mg 3 times a day

Paediatric

Nausea and vomiting in GI disorders, vomiting associated with radiotherapy and cytotoxic chemotherapy, aid to GI intubation, gastro-oesophageal reflux, gastroparesis, nausea and vomiting in migraine, oral or IM or slow IV (over 15 minutes)

Infant (up to 10 kg): 100 micrograms/kg (maximum 1 mg) twice daily

Child 1–3 years (10–14 kg): 1 mg 2–3 times daily

Child 3–5 years (15–19 kg): 2 mg 2–3 times daily

Child 5–9 years (20–29 kg): 2.5 mg three times daily

Child 9–12 years (30 kg and over): 5 mg three times daily (usual maximum 500 micrograms/kg daily)

Pre- and postoperatively, oral or IM or slow IV (over 15 minutes)

Child all ages: 0.1–0.2 mg/kg per dose 3–4 times daily as needed

Contraindications: GI obstruction, haemorrhage or perforation, 3–4 days after GI surgery, convulsive disorders, phaeochromocytoma, previous extrapyramidal reaction.

Precautions: Hepatic impairment, renal impairment,

may mask underlying disorders such as cerebral irritation, epilepsy, depression, porphyria.

Hepatic impairment: Reduce dose.

Renal impairment: Mild impairment: reduce dose to 75% of dose recommended for indication.

» Moderate impairment: reduce dose to 50% of dose recommended for indication.

» Severe impairment: reduce dose to 25–50% of dose recommended for indication.

Adverse effects: Common: Akathisia, drowsiness, dizziness, headache.

Depression, extrapyramidal symptoms including tardive dyskinesia, hypertension, hypotension, hyperprolactinaemia leading to galactorrhoea, diarrhoea, constipation.

Rare: Neuroleptic malignant syndrome, rash, pruritus, oedema, cardiac conduction abnormalities following IV administration, methaemoglobinaemia (more severe in G6PD deficiency), agranulocytosis, hyperaldosteronism.

Interaction with other medicines (*indicates serious):

Absorption of some drugs may be altered due to increased gastric motility caused by metoclopramide.

Acetylsalicylic acid: enhanced effect of acetylsalicylic acid (increased rate of absorption).

Atropine: antagonism of effect of metoclopramide on GI activity.

Chlorpromazine: increased risk of extrapyramidal effects.

* Ciclosporin: plasma ciclosporin concentration increased.

Codeine: antagonism of effect of metoclopramide on GI activity.

Haloperidol: increased risk of extrapyramidal effects.

Methadone: antagonism of effect of metoclopramide on GI activity.

Morphine: antagonism of effect of metoclopramide on GI activity.

Paracetamol: increased absorption of paracetamol.

Suxamethonium: enhanced effects of suxamethonium.

Notes:

» WHO age/weight restriction: not for use in neonates.

Olanzapine

ATC code: N05AH03

Tablet, 5 mg, LOU 5

Indications and dose

Adult

Prevention of chemotherapy-induced acute and delayed nausea or vomiting (high emetogenic IV chemotherapy): 5 or 10 mg on day of chemotherapy (day 1), followed by 5 or 10 mg once daily on days 2 to 4, in combination with other antiemetics

Prevention of chemotherapy-induced acute and delayed nausea or vomiting (moderate emetogenic IV chemotherapy): 5 or 10 mg on day of chemotherapy (day 1), followed by 5 or 10 mg once daily on days 2 to 3, in combination with other antiemetics

Chemotherapy-induced breakthrough nausea or vomiting: 5 to 10 mg once daily for 3 days

Paediatric

Children ≥3 years and adolescents:

Prevention of chemotherapy-induced acute and delayed nausea or vomiting (high and moderate emetogenic IV chemotherapy):

0.1mg/kg/dose to 0.14 mg/kg/dose once daily (may be increased to twice daily); dose rounded to nearest 1.25 mg; maximum 10mg/dose on day of chemotherapy (day 1), and on days 2 to 4, in combination with other antiemetics

Precautions: High doses in elderly. susceptibility to QT interval prolongation

Hepatic impairment: caution in moderate to severe impairment (risk of increased exposure).

Renal impairment: may require dose reduction in renal impairment.

Adverse Effects: Common: Anticholinergic syndrome, appetite increased, arthralgia, asthenia, eosinophilia, fever, glycosuria, oedema, sexual dysfunction

Abdominal distension, alopecia, breast enlargement, diabetes mellitus, dysarthria, epistaxis, memory loss, photosensitivity reaction, urinary disorders

Rare: Hepatic disorders, hypothermia, pancreatitis, rhabdomyolysis, thrombocytopenia

Interaction with other medicines (*indicates serious)

*Anti-Parkinson Agents (Dopamine Agonist): Antipsychotic Agents (Second Generation [Atypical]) may diminish the therapeutic effect of Anti-Parkinson Agents (Dopamine Agonist).

*Azelastine (Nasal): May enhance the CNS depressant effect of CNS Depressants.

*Benzodiazepines: OLANZapine may enhance the adverse/toxic effect of Benzodiazepines.

*Cabergoline: May diminish the therapeutic effect of Antipsychotic Agents. Avoid combination

*Carbamazepine: May decrease the serum concentration of Olanzapine.

*ClozaPine: Anticholinergic Agents may enhance the constipating effect of CloZAPine.

*Domperidone: QT-prolonging Agents (Moderate Risk) may enhance the QTc-prolonging effect of Domperidone.

*Ipratropium (Oral Inhalation): May enhance the anticholinergic effect of Anticholinergic Agents.

*Metoclopramide: May enhance the adverse/toxic effect of Antipsychotic Agents.

*Opioid Agonists: CNS Depressants may enhance the CNS depressant effect of Opioid Agonists.

*Potassium chloride: Anticholinergic agents may enhance the ulcerogenic effect of potassium chloride.

*Potassium citrate: Anticholinergic agents may

enhance the ulcerogenic effect of potassium citrate.

*Thalidomide: CNS depressants may enhance the CNS depressant effect of thalidomide.

Thiazide and thiazide-like diuretics: Anticholinergic agents may increase the serum concentration of thiazide and thiazide-like diuretics.

*Tiotropium: Anticholinergic agents may enhance the anticholinergic effect of tiotropium.

*Zolpidem: CNS Depressants may enhance the CNS depressant effect of zolpidem.

Ondansetron

ATC code: A04AA01

Injection, 2 mg/mL as HCl in 2-mL amp, LOU 2

Oral liquid, 4 mg/5 mL, LOU 2

Tablet, 4 mg, LOU 2

Indications and dose

Adult

Prevention of chemotherapy-induced nausea and vomiting, single-day IV chemotherapy regimens

Highly emetogenic chemotherapy

IV: 8 mg or 0.15 mg/kg administered over 15 minutes 30 minutes prior to chemotherapy then 4 and 8 hours after first dose (maximum 16mg)

Tablet and oral solution: 8 mg started 30 minutes before chemotherapy then every twelve hours for 1 to 2 days after chemotherapy (Alternative dosing of 24mg administered 30 minutes before chemotherapy)

Used in combination with other antiemetics

Moderately emetogenic chemotherapy

IV: 8 mg or 0.15 mg/kg as a single dose; maximum: 16 mg/ dose administered prior to chemotherapy

Oral: 8 mg started 30 minutes before chemotherapy then every twelve hours for 1 to 2 days after chemotherapy

Used in combination with other antiemetics

Low emetogenic chemotherapy

IV**:** *8 mg as a single dose prior to chemotherapy*

Oral**:** *8 mg as a single dose prior to chemotherapy*

Prevention of postoperative nausea and vomiting, moderate- to high-risk patients

IV: 4 mg as a single dose before anaesthesia or at the end of surgery OR

Oral: 8 to 16mg as a single dose given 30 to 60 minutes before anaesthesia

Prevention of radiation therapy-associated nausea and vomiting, high and moderately-emetogenic risk radiation therapy, IV or oral: 8 mg (maximum: 16 mg/dose) once daily or twice daily prior to each fraction of radiation, administer in combination with dexamethasone

Paediatric

Prevention of chemotherapy-induced nausea and vomiting

Highly emetogenic chemotherapy

Infants, children, and adolescents, IV, oral: 0.15 mg/ kg/dose (5 mg/m2/dose), administer first dose before the start of chemotherapy and then every 8 hours (maximum dose 8 mg/dose) used in combination with other antiemetics.

Moderately emetogenic chemotherapy

Infants, children, and adolescents, IV, oral**:** 0.15 mg/kg/dose (5 mg/m2/dose); maximum dose 8 mg/dose; administer first dose before the start of chemotherapy with subsequent doses every 12 hours used in combination with other antiemetics.

Low emetogenic chemotherapy

Infants, children, and adolescents, IV, oral: 0.3 mg/ kg/dose once (10 mg/m2/dose), maximum dose 16 mg/dose, administered 30 minutes before the start of chemotherapy

Postoperative nausea and vomiting prevention

Infant and child ≤40 kg, IV: 0.1 mg/kg/dose as a single dose, maximum dose 4 mg/dose

Child >40 kg, IV: 4 mg/dose as a single dose

Adolescent: IM, IV: 4 mg/dose as a single dose

Radiation-induced nausea and vomiting prevention

Infant ≥5 months, child, and adolescent, oral: 0.2 mg/ kg/dose (maximum dose 8 mg/dose) administered every 8 hours throughout total body irradiation

Acute gastroenteritis, IV

Infant and child IV: 0.15 or 0.3 mg/kg/dose once, maximum dose 16 mg/dose

Acute gastroenteritis, oral

Infant ≥6 months and child ≤10 years, weighing ≤8 kg: 0.15mg/kg/dose once

Child 8 to 15 kg, oral: 2 mg/dose once

Child >15 to 30 kg, oral: 4 mg/dose once

Child >30 kg, oral: 8 mg/dose once

Precautions: Phenylketonuria (some dosage forms (wafers or tablets) contain aspartame), hepatic impairment, prolonged QT interval or risk factors for prolonged QT interval.

Hepatic impairment: Moderate and severe impairment: reduce dose.

Renal impairment: No dose reduction required.

Adverse effects: Common: Constipation, headache, transient rise in hepatic aminotransferases.

Hiccups, hypotension, chest pain, diarrhoea.

Rare: Hypersensitivity reactions (including anaphylaxis), arrhythmias, ECG changes, extrapyramidal effects, seizures, transient visual disturbances, e.g., blurred vision (with rapid IV administration).

Interaction with other medicines (*indicates serious):

Rifampicin: may increase metabolism of ondansetron, increase dose if necessary.

Notes:

- Administration:
  - For slow IV injection, give over 2–5 minutes.
  - For IV infusion, dilute to a concentration of 320–640 micrograms/mL with glucose 5% or sodium chloride 0.9%, give over at least 15 minutes.
- WHO age/weight restriction: > 1 month.
- In patients at moderate risk, may combine ondansetron with other prophylactic interventions. In patients at high risk, combine 3 or more interventions
- Routine use of ondansetron is not recommended in most cases of acute gastroenteritis

Palonosetron

ATC code: A04AA05

Injection, 0.05mg/ml, 5ml vial, Lou 4

Indications and dosage

Adult

Prevention of chemotherapy-induced Nausea and Vomiting, single-day IV chemotherapy regimens

Moderately emetogenic chemotherapy: 0.025mg palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Palonosetron solution for injection should be injected over 30 seconds.

Severe emetogenic chemotherapy

0.025mg palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Palonosetron solution for injection should be injected over 30 seconds.

Paediatric

Prevention of chemotherapy-induced nausea and vomiting (moderately and highly emetogenic)

Children and Adolescents (aged 1 month to 17 years):

20 micrograms/kg (the maximum total dose should not exceed 1.5mg) palonosetron administered as a single 15 minute intravenous infusion beginning approximately 30 minutes before the start of chemotherapy.

Child<1month: Safety and efficacy not established.

Contraindications: Hypersensitivity to the active substance or to any of the excipients

Precautions: History of constipation or signs of bowel obstruction, history of QT prolongation, electrolyte abnormalities, congestive heart failure, bradyarrhythmia, conduction disturbances, patients taking anti-arrhythmic agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities such as hypokalemia and hypomagnesemia.

Hepatic and Renal impairment: Dose adjustment not necessary.

Pregnancy and breastfeeding: Avoid as no information is available.

Adverse effects: Prolonged QT interval, Constipation, Hyperkalaemia, Headache, dizziness, diarrhoea, pruritus, AV block

Interactions with other medicine (*indicates serious)
*Apomorphine- avoid due to risk of severe hypotension
*SNRIs and SSRIs- amitryptilline, escitalopram- risk of serotonin syndrome

Notes

- Efficacy maybe enhanced by administration of a corticosteroid prior to chemotherapy.

19.3. Anti-Inflammatory Medicines

Mesalazine

ATC code: A07EC02

Tablet (ec): 400 mg, LOU 4

Suppository: 1g, LOU 5

Enema: 4g/60ml, LOU 5

Indications and dose

Adult

Treatment of mild to moderate ulcerative colitis, acute attack,

oral: 2.4g daily in divided doses

Maintenance of remission of ulcerative colitis and Crohn's ileocolitis

Oral: 1.2 – 2.4g daily in divided doses

Suppository: 1g daily for 2-4 weeks

Enema: 2g daily at bedtime for 4-6weeks

Paediatric

Treatment of mild to moderate ulcerative colitis, acute attack, oral:

Child 12 – 17 years: oral, 800mg 2 – 3 times daily. Enema, 2g once daily at bedtime

Maintenance of remission of ulcerative colitis and Crohn's ileocolitis:

Child 12 – 17 years: oral, 400 – 800mg 2 – 3 times daily

Enema, 2g daily at bedtime

Contraindications: Hypersensitivity, Blood clotting abnormalities, severe renal/hepatic impairment.

Precautions: Elderly, maintain adequate fluid intake, pulmonary disease

Hepatic impairment: Caution in mild to moderate impairment, avoid in severe impairment.

Renal impairment: In adults and children. Use with caution. Avoid if eGFR less than 20 mL/min/1.73 m2.

Pregnancy: Treatment can be continued without interruption

Breastfeeding: Diarrhoea reported in breastfed infants. Monitor breastfed infants for diarrhoea.

Adverse Effects: Common: Rash, abdominal pain, diarrhea, N/V, arthralgia, headache,

Rare: Cholestasis exacerbated, drug fever, flatulence, nephritis, constipation (with rectal use), SJS, haematological disorders, renal impairment, photosensitivity, hepatotoxicity.

Interaction with other medicines (*indicates serious)

*Antacids: May diminish the therapeutic effect of Mesalamine.

Heparins: 5-Aminosalicylic Acid Derivatives may enhance the adverse/toxic effect of Heparin.

Myelosuppressive Agents: 5-Aminosalicylic Acid Derivatives may enhance the myelosuppressive effect.

Nonsteroidal Anti-Inflammatory Agents: May enhance the nephrotoxic effect of 5-Aminosalicylic Acid Derivatives.

Thiopurine Analogs: 5-Aminosalicylic Acid Derivatives may enhance the myelosuppressive effect of Thiopurine Analogs. 5-Aminosalicylic Acid Derivatives may increase serum concentrations of the active metabolite(s) of Thiopurine Analogs.

*Varicella Virus-Containing Vaccines: 5-Aminosalicylic Acid Derivatives may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines.

Notes

Mesalazine enema and suppositories are more effective than dose intensification of oral mesalazine

Prednisolone

ATC code: H02AB06

Tablet, 5 mg LOU 4

Indications and dose

Adult

Steroid-sparing agents (e.g., biologic agents, immunomodulators) should be introduced with the goal of discontinuing corticosteroid therapy as soon a possible.

Inflammatory bowel disease, Crohn disease (moderate to severe or select patients with mild disease), induction, oral (not for long-term use): 40 to 60 mg once daily for 7 to 14 days, followed by a taper of up to 3 months (e.g., reduce dose by 5 mg/day at weekly intervals until 20 mg/day is reached, then further reduce by 2.5 to 5 mg/day at weekly intervals)

Ulcerative colitis (moderate to severe), induction, oral (not for long-term use): 40 to 60 mg/day in 1 to 2 divided doses. Taper over 1 to 3 months depending on symptoms

Paediatric

Ulcerative colitis, moderate to severe (not for long-term maintenance, use for induction only), oral

Child and adolescent: 1 to 2 mg/kg/day administered in the morning for 2 to 3 weeks, maximum daily dose 60 mg/day; if no response after 7 to 14 days optimal dosing and compliance should be assessed; after the initial 2 to 3 weeks, the dose is gradually decreased over 8 to 10 weeks

Contraindications: Untreated systemic infection, administration of live vaccines: usually not relevant to emergency treatment.

Precautions: Most precautions do not apply for emergency or short-term use.

Increased severity of viral infections, recent MI, congestive heart failure, renal impairment, hepatic impairment, diabetes mellitus, osteoporosis, glaucoma, corneal perforation, severe psychosis, epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy.

Hepatic impairment: Adverse effects more common.

Renal impairment: Dose reduction not necessary.

Adverse effects: Incidence of adverse effects is related to dose and duration of treatment. Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.

Common: Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects (including euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour).

Rare: Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions including anaphylaxis, psychiatric effects (including delirium and psychosis).

Interaction with other medicines (*indicates serious):

* Amphotericin B: increased risk of hypokalaemia.

Antacids: may reduce the bioavailability of corticosteroids (consider separating dose > 2 hours)

* Carbamazepine: accelerated metabolism of prednisolone (reduced effect).

BCG: reduced the therapeutic effect

Ciclosporin: increased plasma concentration of prednisolone.

Contraceptives, oral: oral contraceptives containing estrogens increase plasma concentration of prednisolone.

Desmopressin: enhanced the hyponatremic effect

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of prednisolone.

Furosemide: antagonism of diuretic effect, increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect, increased risk of hypokalaemia.

Lefluomide: enhanced haematological toxicity (thrombocytopenia, agranulocytopenia)

measles, mumps and rubella virus vaccine: enhanced adverse effects - Avoid concurrent use

Neuromuscular blockers: may enhance adverse neuromuscular effect of corticosteroids (muscle weakness, myopathies). Use the lowest dose and for the shortest duration possible

NSAIMs: increased risk of GI bleeding and ulceration, prednisolone reduces plasma salicylate concentration.

Tacrolimus (topical): may enhance toxicity of immunosuppressant.

19.4. Laxatives

Bisacodyl

ATC code: A06AB02

Tablet, 5 mg, LOU 2

Suppository, 5 mg, LOU 2

Indications and dose

Adult

Constipation,

Oral: 5 to 15 mg once daily

Rectal, Suppository: 10 mg once daily

Paediatric

Constipation, oral

Child ≥3 years to <10 years: 5 mg once daily

Child 10 to <12 years: 5 to 10 mg once daily

Child ≥12 years and adolescents: 5 to 15 mg once daily

Constipation, rectal

Child 2 to ≤10 years: 5 mg (1/2 suppository) once daily

Child >10 years and adolescents: 5 to 10 mg once daily

Contraindications: Acute abdominal conditions, acute inflammatory bowel disease, intestinal obstruction, severe dehydration

Precautions: Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia, prolonged use may harm intestinal function, risk of electrolyte imbalance with prolonged use

Adverse Effects: Common: GI discomfort, nausea, haematochezia, vomiting

Rare: Angioedema, colitis, dehydration

Interaction with other medicines (*indicates serious)

*Antacids: May diminish the therapeutic effect of Bisacodyl.

Polyethylene Glycol-Electrolyte Solution: Bisacodyl may enhance the adverse/toxic effect of Polyethylene Glycol-Electrolyte Solution.

*Sodium sulphate: Laxatives (stimulants) may enhance the adverse/toxic effect of sodium sulphate.

Notes:

- To be administered at night
- Not to be administered within one hour of dairy products or antacid

Lactulose

ATC code: A06AD11

Oral liquid, 3.1–3.7 g/5 mL, LOU 4

Indications and dose

Adult

Constipation, oral: Initially 15 mL twice daily, adjusted according to response

Hepatic encephalopathy (portal systemic encephalopathy), oral: Adjusted according to response to 30–50 mL 3 times a day, subsequently adjusted to produce 2–3 soft stools per day

Paediatric

Constipation, oral

Child 1–11 months: 2.5 mL twice daily, adjusted according to response

Child 1–4 years: 2.5–10 mL twice daily, adjusted according to response

Child 5–17 years: 5–20 mL twice daily, adjusted according to response

Hepatic encephalopathy (portal systemic encephalopathy), oral

Child 12–17 years: Adjusted according to response to 30–50 mL 3 times a day, subsequently adjusted to produce 2–3 soft stools per day

Contraindications, Galactosaemia, GI, obstruction, GI perforation, risk of GI perforation, diarhoea

Precautions: Lactose/Galactose intolerance (use with caution in patients with DM), electrolyte imbalance (hyponatremia).

Hepatic Impairment, No dose adjustment required

Renal Impairment, No dose adjustment required

Pregnancy: Not known to be harmful.

Adverse effects: Common, Epigastric pain, diarrhea, flatulence, nausea, vomiting, bloating, cramps.

Rare, Electrolyte imbalance (hypernatremia, hypokalemia, dehydration)

Interaction with other medicines: Do not use with other laxative (hepatic encephalopathy),

Increased chance of GI obstruction with nifedipine

May enhance anticoagulant effect of vitamin K

Note:

- Lactulose may take up to 48 hours to act.

19.5. Medicines Used In Diarrhoea

19.5.1. Oral Rehydration

Oral Rehydration Salts (ORS)

ATC code: A07CA

Powder for dilution to make 500 mL, LOU 1

Contains: glucose 13.5 g/L, sodium chloride 2.6 g/L, potassium chloride 1.5 g/L, trisodium citrate dihydrate 2.9 g/L

Provides: glucose 75 mmol/L, sodium 75 mEq or mmol/L, chloride 65 mEq or mmol/L, potassium 20 mEq or mmol/L, citrate 10 mmol/L, osmolarity 245 mOsm/L

Indications and dose

Adult

Replacement of fluids and electrolytes in acute diarrhoea, oral: 200–400 mL solution after every loose motion

Paediatric

Replacement of fluids and electrolytes in acute diarrhoea: WHO-recommended plans A, B, and C should be followed (appendix 3).

Precautions: Renal impairment.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction may be necessary, monitor electrolytes carefully.

Adverse effects: Vomiting may indicate too rapid administration, hypernatraemia and hyperkalaemia may result from overdose in renal impairment or administration of too concentrated a solution.

Interaction with other medicines:

There are no known interactions where it is recommended to avoid concomitant use.

Zinc Sulphate (Co-Packed With ORS)

ATC code: A12CB01

Tablet (dispersible), 20 mg, LOU 2

Indications and dose

Paediatric

Adjunct to oral rehydration therapy in acute diarrhoea, oral

Infant under 6 months: 10 mg (elemental zinc) daily for 10–14 days

Infant or **child over 6 months:** 20 mg (elemental zinc) daily for 10–14 days

Precautions: Acute renal failure (may accumulate).

Hepatic impairment: Dose reduction not necessary.

Renal impairment: May accumulate in acute renal failure.

Adverse effects: Abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, gastritis, irritability, headache, lethargy.

Interaction with other medicines:

Calcium salts: reduced absorption of zinc sulphate.

Ciprofloxacin: reduced absorption of ciprofloxacin.

Ferrous salts: absorption of zinc and of oral ferrous salts reduced.

Ofloxacin: reduced absorption of ofloxacin.

Penicillamine: absorption of both drugs reduced.

Notes:

- Zinc sulphate tablets may be dispersed in breast milk, in oral rehydration solution or in water on a small spoon, older children may chew tablets or swallow them with water.
- Administer with food if GI upset occurs.

Rehydration Solution For Malnutrition (RESOMAL)

ATC code: A07CA

Powder for oral dilution to make 1 L (42 g) (WHO formula), LOU 4

Indications and dose

Rehydration and correction of electrolyte derangements in severe acute malnutrition (SAM) in children

Note: The standard ORS solution (90 mmol sodium/L) contains too much sodium and too little potassium for severely malnourished children. Instead give special ReSoMal.

It is difficult to estimate dehydration status in a severely malnourished child using clinical signs alone. Assume all children with watery diarrhoea may have dehydration and give:

- ReSoMal 5 mL/kg every 30 min. for two hours, orally or by nasogastric tube, then
- 5–10 mL/kg/h for next 4–10 hours; exact amount to be given should be determined by how much the child wants, stool loss, and vomiting. Replace the ReSoMal doses at 4, 6, 8, and 10 hours with F-75 if rehydration is continuing at these times, then
- Continue feeding starter F-75

To prevent dehydration when a child has continuing watery diarrhoea:

- Keep feeding with starter F-75
- Replace approximate volume of stool losses with ReSoMal. As a guide give 50–100 mL after each watery stool. (Note: It is common for malnourished children to pass many small unformed stools; these should not be confused with profuse watery stools and do not require fluid replacement.)
- If the child is breastfed, encourage that to continue

Contraindications: Do not administer to patients with cholera or uncomplicated acute malnutrition: use standard ORS instead.

Precautions: May cause heart failure when administered too rapidly. During treatment, closely monitor the rate of administration to avoid overhydration. Increase in respiratory and pulse rates and appearance or increase of oedema are signs of over rapid rehydration. In this event, stop ReSoMal for one hour then reassess the patient's condition.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction may be necessary, monitor electrolytes carefully.

Interaction with other medicines:

There are no known interactions where it is recommended to avoid concomitant use.

19.6. Vasoconstrictor Medicines

Terlipressin

ATC Code: H01BA04

Injection, 1mg (as acetate) in 8.5ml solution, LOU4

Indications and Dose:

Adult

Treatment of bleeding oesophageal varices (Emergency treatment until endoscopic therapy is available and as adjuvant therapy to endoscopic haemostasis, IV injection (over 1 minute):

Initially 1-2 mg terlipressin acetate (equivalent to 1-2 ampoules of Terlipressin Acetate 1mg solution for injection).

Depending on the patient's body weight the dose can be adjusted as follows:

weight less than 50 kg: 1 mg (1 ampoule of 8.5 ml)

weight 50 kg to 70 kg: 1.5 mg (1.5 ampoules of 8.5 ml)

weight exceeding 70 kg: 2 mg (2 ampoules of 8.5 ml)

After the initial injection, the dose can be reduced to 1 mg every 4 to 6 hours.

Dosing considerations:

Maximum daily dose is 120 micrograms/kg body weight.

Treatment is limited to 2 – 3 days in adaptation to the course of the disease.

used with caution in patients over 70 years.

Children and adolescents

Insufficient data on safety and efficacy

Contraindications:

Hypersensitivity to the active substance or to any of the excipients

Precautions:

Septic shock, bronchial asthma, respiratory deficiencies, uncontrolled hypertension, cerebral or peripheral vascular diseases, cardiac arrhythmias, cardiac insufficiency

coronary deficiencies or previous myocardial infarction, chronic renal insufficiency, hypovolaemia, hyponatraemia, hypokalaemia.

Hepatic impairment:

Dose adjustment is not required.

Renal impairment:

Use with caution in patients with chronic renal failure.

Pregnancy:

Use is not recommended during pregnancy as it has been shown to cause uterine contractions and increased intrauterine pressure in early pregnancy and may decrease uterine blood flow.

Breast-feeding: Limited data

Adverse effects:

hyponatraemia if fluid not monitored, hyperglycaemia, headache, triggering of a convulsive disorder, stroke, ventricular and supra-ventricular arrhythmia, bradycardia, signs of ischaemia in the ECG, angina pectoris, acute hypertension rise, in particular in patients already suffering from hypertension (generally, it decreases spontaneously), atrial fibrillation, ventricular extrasystoles, tachycardia, chest pain, myocardial infarction, fluid overload with pulmonary oedema, cardiac failure, Torsade de Pointes, myocardial ischemia, hypertension, hypotension, peripheral ischaemia, peripheral vasoconstriction, facial pallor, intestinal ischaemia, peripheral cyanosis, hot flushes, pain in the chest, bronchospasm, respiratory distress, respiratory failure, dyspnoea, transient abdominal cramps, transient diarrhoea, transient nausea, transient vomiting, paleness, lymphangitis,
skin necrosis unrelated to the site of administration, injection site necrosis, uterine constriction, decreased uterine blood flow, uterine hypertonus, uterine ischemia, abdominal cramps (in women)

Interactions with other medicines:

non-selective β-blockers, propofol, sufentanil, medications that can prolong the QT interval, such as class IA and III antiarrhythmics, erythromycin, certain antihistamines and tricyclic antidepressants or medications that may cause hypokalaemia or hypomagnesemia.

Note:

» Specialist use in facilities with ability to have regular monitori ng of the cardiovascular system, haematology and electrolytes.

19.7. Medicines Used For Ascites & GI Bleeding

Propranolol

ATC code : C07AA05

Tablet, 20mg,40mg, LOU 4

Indications and dose

Adults

Prophylaxis of variceal bleeding in portal hypotension: Initially 40 mg twice daily, then increased to 80 mg twice daily (max. per dose 160 mg twice daily), dose to be adjusted according to heart rate

Contraindications: *Refer to 8.2*

Precautions: *Refer to section 8.2*

Hepatic and renal impairment: *Refer to section 8.2*

Pregnancy and Breastfeeding: *Refer to section 8.2*

Adverse effects: *Refer to section 8.2*

Interactions with other medicines: *Refer to section 8.2*

Spironolactone

See Spironolactone section 18

Vasopressin

ATC code: H01BA01

Solution for injection, 20 units/mL, LOU 5

Indications and dose

Adults

Management of ascites and gastroesophageal variceal hemorrhage; initial control of oesophageal variceal bleeding (other agents such as octreotide are preferred), continuous infusion: 0.2 to 0.4 units/min, max. 0.8 units/min

Paediatric

Adjunct in acute massive haemorrhage of GI tract or oesophageal varices (specialist use only), in portal hypertension by continuous IV infusion

Child all ages: Initially 0.3 unit/kg (max. per dose 20 units), dose to be administered over 20–30 minutes, then 0.3 unit/kg/hour, adjusted according to response (max. per dose 1 unit/kg/hour); if bleeding stops, continue at same dose for 12 hours, then withdraw gradually over 24–48 hours; max. duration of treatment 72 hours; dose may alternatively be infused directly into the superior mesenteric artery

Contraindications: Hypersensitivity, Chronic nephritis (until reasonable blood nitrogen concentrations attained), vascular disease (especially disease of coronary arteries) unless extreme caution

Precautions: Asthma, avoid fluid overload, conditions which might be aggravated by water retention,

epilepsy, heart failure, hypertension, migraine

Hepatic impairment: No dosage adjustment recommended

Renal Impairment: No dosage adjustment recommended

Pregnancy: dose adjustment may be needed due to oxytocic effect in third trimester and increased clearance

Breastfeeding: unknown harm, better to avoid

Adverse Effects: Common: bradyarrythmia, tachyarrythmia, hyponatremia, fluid imbalance

Serious/Rare: Atrial fibrillation, hypertension, cardiac arrest, ischemic heart disease angina pectoris, bronchospasm, Pulmonary Embolism, gangrene, limb ischemia (distal), low cardiac output, right heart failure, shock (hemorrhagic), Skin lesion (ischemic), mesenteric ischemia, decreased platelet count, increased serum bilirubin, renal insufficiency.

Interaction with other medicines:

Alpha-/Beta-Agonists (Direct-Acting): May enhance the hypertensive effect of Vasopressin.

Drugs Suspected of Causing Diabetes Insipidus: May diminish the therapeutic effect of Vasopressin.

Drugs Suspected of Causing SIADH: May enhance the therapeutic effect of Vasopressin.

Notes:

» Administration: diluted in 100 mL NS/dextrose 5% and infuse over a 15 minutes (conc. 0.1unit/mL or 1unit/mL)

During and after discontinuation of therapy monitor closely serum and urine sodium/urine output levels.

20.Medicines For Endocrine Disorders

20.1. Adrenal Hormones & Synthetic Substitutes

Fludrocortisone

ATC code: H02AA02

Tablet,100 micrograms (0.1 mg) as acetate, LOU 4

Indications and dose

Adult

Partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease, treatment of salt-losing adrenogenital syndrome, mineralocorticoid replacement in adrenocortical insufficiency, orthostatic hypotension: 0.1–0.2 mg/day with dose ranges of 0.1 mg three times/ week to 0.2 mg/day

Addison's disease: Initial, 0.1 mg/day; if transient hypertension develops, reduce dose to 0.05 mg/day (preferred administration with cortisone [10–37.5 mg/ day] or hydrocortisone [10–30 mg/day])

Salt-losing adrenogenital syndrome: 0.05 mg–0.2 mg/day in 1 or 2 divided doses

Paediatric

Adrenocortical insufficiency/Addison's disease, Oral

Child all ages: 50–100 micrograms per daily in single daily dose or divided every twelve hours; Used in combination with sodium chloride supplementation

Congenital adrenal hyperplasia, Oral

Child all ages: 50 to 300micrograms per day; dose adjusted according to response

Contraindications: History of possible or known hypersensitivity to fludrocortisone, Congestive cardiac failure, systemic fungal infections.

Precautions: Dosage should be tapered gradually if therapy is discontinued, use with caution in patients with hypertension, diabetes, oedema or renal impairment, seizure disorders, osteoporosis.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Use with caution. Dose reduction not necessary.

Adverse effects: When used as mineralocorticoid replacement, adverse effects usually indicate that the dose (and/or salt intake) is too high.

Common: Sodium and water retention, oedema, hypokalaemia, hypertension, Bruising symptom, Impaired wound healing, Petechiae, drug-induced myopathy, muscle weakness, vertigo, headache, irregular periods, peptic ulcer disease, swollen abdomen.

Rare: Hypokalaemic alkalosis, hyperglycemia, glycosuria, seizure, raised ICP, heart failure.

Interaction with other medicines (*indicates serious):

*BCG – therapeutic effects of BCG are diminished by immunosuppressant

*Desmopressin – hyponatremic effect is enhanced by corticosteroids

Leflunomide – adverse/toxic effects are enhanced by immunosuppressant (specifically the risk for heamatological toxicity, e.g., Thrombocytopenia. agranulocytosis)

Antacids – may increase bioavailability of corticosteroids

Aprepitant – may increase serum concentration of corticosteroids

Immunosuppressants (e.g., Bricitinib, Tacrolimus etc – may enhance immunosuppressive effects of corticosteroids

Mifepristone – may diminish the therapeutic effects of corticosteroids.

Systemic corticosteroids (such as fludrocortisone) reduce potassium concentration and increase risk of hypokalaemia. Administration with other drugs which also reduce potassium concentration may increase this risk, monitor potassium concentration and give supplements if necessary.

Phenytoin: increases metabolism of fludrocortisone and may reduce its activity, monitor clinical effect and increase corticosteroid dose if necessary (large increases may be needed). Metabolism of phenytoin may be affected.

Rifampicin: increases metabolism of fludrocortisone and may reduce its activity, monitor clinical effect and increase corticosteroid dose if needed (may need to double dose).

Warfarin: fludrocortisone may increase warfarin's anticoagulant effect, increasing the risk of bleeding, monitor INR and decrease warfarin dose if necessary.

Notes:

» Synthetic glucocorticoids include betamethasone, dexamethasone and prednisolone. Although fludrocortisone [not included on the 15th WHO Model List] also has glucocorticoid properties, it is used for its potent mineralocorticoid effects.

Hydrocortisone

ATC code: H02AB09

Tablet, 5 mg, 20 mg, LOU 4

Powder for injection (as hydrocortisone sodium succinate), 100 mg, LOU 4

Indications and dose

Adult

Adrenocortical insufficiency resulting from septic shock, IV: 50 mg every 6 hours, given in combination with fludrocortisone

Corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of minor surgery under general anaesthesia, IV or IV infusion: Initial 20-25 mg; to be administered at induction of surgery, the patient's usual oral

corticosteroid dose is recommenced after surgery.

Corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of moderate or major surgery, IV or IV infusion: Initially 20-50 mg to be administered at induction of surgery (following usual oral corticosteroid dose on the morning of surgery), followed by (by intravenous injection) 25-50 mg 3 times a day for 24 hours after moderate surgery and 48-72 hours after major surgery

Replacement therapy in adrenocortical insufficiency in Addison's disease or following adrenalectomy, oral: 15–30 mg daily in divided doses with largest dose in the morning upon awakening (usually 20 mg in the morning and 10 mg in early evening). Sometimes given together with NaCl or 50–300 micrograms of fludrocortisone daily.

Replacement therapy in adrenocortical insufficiency, by IM injection, slow IV injection, or IV infusion: 100–500 mg 3–4 times a day or when required

Paediatric

Adrenocortical insufficiency, oral:

Child all ages: Initial dose: 8 to 10 mg/m2/day divided every 8 to 12 hours, dose should be individualized using lowest possible dose.

Addison disease, adrenal hypoplasia, chronic maintenance or replacement therapy, oral **Neonate, infant** or **child:** Usual dose 4–5 mg/m2 every 8 hours. Higher doses may be needed.

Note: Give larger doses in the morning and smaller doses in the evening.

Acute Adrenal Crisis, IV

>1 month to 1 year: 25mg then 50mg/ m2/day by continuous Iv infusion or divided every 6 to 8 hours

Alternative: 1 – 2mg/kg IV bolus then 25 – 150mg/day IV divide every 6 to 8 hours

1 to 12 years:50 – 100mg rapid IV bolus, then 50mg/ m2/day by continuous IV infusion or in divided doses every 6 to 8 hours

Alternative: 1 – 2mg/kg IV bolus, then 150 – 250mg/ day in divided doses every 6 to 8 hours

Contraindications: Systemic infection (unless specific therapy given), avoid live virus vaccines in patients receiving immunosuppressive doses.

Precautions: Avoid using higher than recommended dose, titrate to lowest effective dose, adrenal suppression, abrupt withdrawal, peptic ulcer disease, psychiatric disorders, glaucoma, osteoporosis, myasthenia gravis, infection, growth restriction, hypertension, congestive heart failure, hepatic impairment, renal impairment, diabetes mellitus, ocular herpes simplex, epilepsy, hypothyroidism, history of steroid myopathy, ulcerative colitis, diverticulitis, recent intestinal anastomoses, thromboembolic disorders, latent TB.

When used in the treatment of adrenal insufficiency, these precautions may not apply, seek specialist advice.

Hepatic impairment: Adverse effects are more common.

Renal impairment: Use with caution. Dose reduction not necessary.

Adverse effects: When used as mineralocorticoid replacement, adverse effects usually indicate that the dose (and/or salt intake) is too high.

Common: Adrenal suppression, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, dyslipidemia, osteoporosis, fractures, increased appetite, dyspepsia, delayed wound healing, skin atrophy, bruising, acne, hirsutism, growth retardation in children, myopathy, muscle weakness and wasting, fat redistribution (producing cushingoid appearance), weight gain, amenorrhoea, increased appetite, disturbances of mood. Osteonecrosis, particularly of the femoral and humeral heads.

Rare: Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions, tendon rupture (especially of the Achilles tendon).

Psychiatric effects Include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium or psychosis are less common.

Interaction with other medicines (*indicates serious):

Acetylsalicylic acid: increased risk of GI bleeding and ulceration, hydrocortisone reduces plasma salicylate concentration.

Amiloride: antagonism of diuretic effect.

*Amphotericin B: increased risk of hypokalemia (avoid concomitant use unless hydrocortisone needed to control reactions).

Atenolol: antagonism of hypotensive effect.

Calcium salts: reduced absorption of calcium salts.

*Carbamazepine: accelerated metabolism of hydrocortisone (reduced effect).

Contraceptives, oral: oral contraceptives containing estrogens increase plasma concentration of hydrocortisone.

Corticosteroids: concurrent use of selected corticosteroids and selected fluoroquinolones may result in an increased risk of tendon rupture.

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: inhibits metabolism of hydrocortisone.

Furosemide: antagonism of diuretic effect, increased risk of hypokalaemia.

Glibenclamide: antagonism of hypoglycaemic effect.

Glyceryl trinitrate: antagonism of hypotensive effect.

Hydralazine: antagonism of hypotensive effect.

Hydrochlorothiazide: antagonism of diuretic effect, increased risk of hypokalaemia.

Ibuprofen: increased risk of GI bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

Metformin: antagonism of hypoglycaemic effect.

*Methotrexate: increased risk of haematological toxicity.

Nifedipine: antagonism of hypotensive effect.

*Phenobarbital: metabolism of hydrocortisone accelerated (reduced effect).

*Phenytoin: metabolism of hydrocortisone accelerated (reduced effect).

Propranolol: antagonism of hypotensive effect.

*Rifampicin: accelerated metabolism of hydrocortisone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with hydrocortisone.

Sodium nitroprusside: antagonism of hypotensive effect.

Spironolactone: antagonism of diuretic effect.

Infuenza vaccine: high doses of hydrocortisone impair immune response.

*Live vaccines: high doses of hydrocortisone impair immune response, avoid use of live vaccines.

*Warfarin: anticoagulant effect possibly enhanced or reduced (high-dose hydrocortisone enhances anticoagulant effect).

Notes:

Withdraw therapy with gradual tapering.

Administer with food or milk to decrease GI upset.

In adrenal replacement therapy, the dose may need to be increased at time of stress or infection, seek specialist advice.

IMPORTANT INFORMATION:

Hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, acute adrenal insufficiency (adrenal crisis) may occur with abrupt withdrawal after long-term therapy (longer than 3 weeks) or with stress, withdrawal and discontinuation of steroids should be performed carefully, patients with HPA axis suppression may require doses of systemic glucocorticosteroids prior to, during and after unusual stress (e.g., surgery). Immunosuppression may occur, patients may be more susceptible to infections, avoid exposure to chickenpox and measles. Corticosteroids may activate latent opportunistic infections or exacerbate systemic fungal infections. May cause osteoporosis (at any age) or inhibition of bone growth in paediatric patients. Acute myopathy may occur with high doses, elevated intraocular pressure may occur (especially with prolonged use), and CNS effects (ranging from euphoria to psychosis) may occur.

20.2. Androgens

Testosterone

ATC code: G03BA03

Gel, 1%, LOU 4

Injection, 250 mg (enanthate) in 1-mL amp, LOU 4

Testosterone is a complementary list androgenic medicine

Indications and dose:

Adult

Hypogonadism (males), by slow IM injection: Initially 250 mg every 2–3 weeks, usual maintenance dose, 250 mg every 3–6 weeks

Hypogonadism (males), topical: Initial, 5 g (contains 50 mg testosterone) applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders or upper arms; may increase dose to 10 g daily after 2 weeks

Paediatric

Hypogonadism, IM

Children over 12: 25–75 mg every 3–4 weeks

Contraindications: Hypersensitivity, breast cancer in men, prostate cancer, hypercalcaemia, pregnancy, breastfeeding, nephrotic syndrome, history of primary liver tumours.

Precautions: cardiac disease, renal impairment, hepatic impairment, the elderly, ischaemic heart disease, hypertension, epilepsy, migraine, diabetes mellitus, skeletal metastases (risk of hypercalcaemia), examine prostate and breast regularly during treatment, prepubertal boys, interactions

Hepatic impairment: Caution - increased risk of fluid retention and heart failure

Renal impairment: Caution—potential for fluid retention.

Adverse effects: prostate abnormalities and prostate cancer, headache, depression, GI bleeding, nausea, polycythaemia, cholestatic jaundice, changes in libido, gynaecomastia, anxiety, asthenia, paraesthesia, electrolyte disturbances including sodium retention with oedema and hypercalcaemia, hypertension, and weight gain, increased bone growth, androgenic effects including hirsutism, male-pattern baldness, seborrhoea, acne, pruritus, priapism, precocious sexual development and premature closure of epiphyses in prepubertal males, virilism in females, and suppression of spermatogenesis in men, rarely liver tumours, sleep apnoea also reported.

Interaction with other medicines:

Vitamin K antagonists (e.g., warfarin): Androgens may enhance the anticoagulant effect of vitamin K antagonists.

Bupropion: lowering of the seizure threshold

Corticosteroids: increased risk of edema

Cyclosporin: increased risk of Cyclosporin toxicity (renal dysfunction, cholestasis, paresthesias)

Glimepiride: increased blood glucose lowering effect and increased risk of hypoglycemia

Insulin: increased risk of hypoglycemia (CNS depression, seizures)

Paclitaxel: increased risk of paclitaxel toxicity

Warfarin and coumarins: increased risk of bleeding

20.3. Estrogens

Conjugated Estrogens

ATC code: G03CA57

Tablet, 0.3 mg, LOU 4

Vaginal cream, 0.625 mg/g base (30 g), LOU 4

Indications and dose

Adult

Atrophic vaginitis, vaginal cream, per vaginal or topically: 1–2 g daily, on a cyclical basis; maximum 4 g/day

Atrophic vaginitis, oral: Initial, 0.3 mg/day; the lowest dose that will control symptoms should be used; may be given cyclically or daily, depending on medical assessment of patient

Menopausal and postmenopausal symptoms, oral: 0.3 to 1.25 mg daily given in conjunction with a cyclic progestogen for 12 to 14 days of each cycle in women with a uterus

Postmenopausal osteoporosis, prophylaxis, oral: Initial, 0.3 mg daily given continuously or in cyclical regimens (e.g., 25 days on, 5 days off); adjust dose based on individual clinical and bone mineral density responses; adjust to lowest level that provides effective control

Primary ovarian failure, oral: 1.25 mg daily

Female hypogonadism, oral: 0.3 or 0.625 mg daily given cyclically (e.g., 3 weeks on, 1 week off); adjust dose depending on the severity of symptoms and responsiveness of endometrium

Paediatric

Safety and efficacy not established

Contraindications: hepatic dysfunction, a history of estrogen dependent neoplasia such as breast or endometrial cancer, endometrial hyperplasia, undiagnosed vaginal bleeding, cerebrovascular accident, thrombosis or thromboembolic disorders, active thrombophlebitis, ophthalmic vascular disease, known or suspected pregnancy.

Precautions: postmenopausal women, endometriosis, asthma, epilepsy, migraine, coronary heart disease, diabetes or renal disorders, gallbladder disease, cholestatic jaundice.

Hepatic impairment: Avoid in acute or active disease

Adverse effects: there may be sodium and water retention with oedema, weight gain, tenderness and enlargement of the breasts, changes in libido, menstrual disorders and withdrawal bleeding, alterations in liver function, jaundice, gallstones, depression, headache, migraine, dizziness, a decrease in glucose tolerance, and decrease in tolerance of contact lenses. Nausea and vomiting and other GI disturbances. Skin reactions, cardiovascular effects (risk in blood pressure).

Interaction with other medicines (*Indicates serious):

*Tranexamic Acid: Estrogen Derivatives may enhance the thrombogenic effect of Tranexamic Acid.
Avoid combination

hydrocortisone, anticoagulants, aminoglutethimide, carbamazepine, phenobarbital, rifampin, nafcillin, nevirapine, phenytoin, ethanol, rifamycins.

Estradiol

ATC code: G03CA03

Transdermal patch, 0.1 mg/day (100 micrograms in 24hours)

Indications and dose

Adult

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women; prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of or contraindicated for other medicines approved for prevention of osteoporosis: Patch to be applied twice weekly (every three to four days); initiated and continued at the lowest effective dose for the shortest duration

Contraindications: hepatic dysfunction, a history of estrogen dependent neoplasia such as breast or endometrial cancer, endometrial hyperplasia, undiagnosed vaginal bleeding, cerebrovascular accident, thrombosis or thromboembolic disorders, active thrombophlebitis, ophthalmic vascular disease, Pophyria.

Precautions: HRT should be initiated for symptoms that adversely affect quality of life. Risk benefit analysis should be done before starting treatment and annually. Close supervision in case of: risk of thromboembolic disorders, risk of estrogen dependent tumours, in hypertension, liver disorders, migraine, SLE epilepsy, asthma.

Hepatic impairment: Avoid in acute or active disease

Pregnancy: Not indicated for use during pregnancy.

Breastfeeding: Not indicated

Conception and contraception: HRT does not provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-estrogen combined oral contraceptive pill to provide both relief of menopausal symptoms and contraception, it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives. If any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary.

Adverse effects: Sodium and water retention with oedema, weight gain, tenderness and enlargement of the breasts, changes in libido, menstrual disorders and withdrawal bleeding, alterations in liver function, jaundice, gallstones, depression, headache, migraine, dizziness, Insomnia, a decrease in glucose tolerance, and decrease in tolerance of contact lenses. Nausea and vomiting and other GI disturbances. Skin reactions, cardiovascular effects (risk in blood pressure), Pain,

Interaction with other medicines:

Tranexamic acid: increased risk of thrombotic events

HIV protease inhibitors, Antiepileptic agents, Bosentan, Nevirapine, Rifampicin, Rifabutin, Efavirenz, Modafinil: predicted to decrease the effects of hormone replacement therapy.

Thalidomide, Pomalidomide, Lenalidomide: increase the risk of venous thromboembolism.

NSAIMs (etoricoxib): slightly increase the exposure to hormone replacement therapy

Oral hormone replacement therapy is predicted to decrease the effects of thyroid hormones

Hormone replacement therapy is predicted to increase the exposure to monoamine-oxidase B inhibitors (selegiline)

20.4. Progestogens

Medroxyprogesterone Acetate

ATC code: G03AC06

Tablet, 5 mg, LOU 4

Indications and dose

Adult

Abnormal uterine bleeding unrelated to menstrual cycle, hormonal imbalance-induced, oral: 5 to 10 mg daily for 5 to 10 days beginning on day 16 or 21 of the menstrual cycle, to produce optimum secretory transformation of the primed endometrium; 10 mg daily for 10 days beginning on day 16 of the cycle

Secondary physiologic amenorrhea, oral: 5 to 10 mg daily for 5 to 10 days, for optimum secretory transformation of the primed endometrium; 10 mg for 10 days, therapy may be started at any time

Paediatric

Not applicable

Contraindications: pregnancy, history of breast cancer (may be used after 5 years if no evidence of current disease), undiagnosed vaginal bleeding, history of pruritus during pregnancy, active liver disease, severe arterial disease, multiple risk factors for venous thromboembolism and arterial disease, porphyria.

Precautions: migraine, liver disease, thromboembolic or coronary vascular disease, diabetes mellitus, hypertension, renal disease,

Hepatic impairment: Avoid in significant liver disease

Renal impairment: Use with caution

Breastfeeding: Present in milk—no adverse effects reported. The benefits of using medroxyprogesterone acetate in breastfeeding women outweigh any risks

Adverse effects: menstrual irregularities, delayed return to fertility, reduction in bone mineral density, weight gain, depression, rarely anaphylaxis, injection-site reactions, breast cancer (small increase in risk of breast cancer)

20.5. Medicines For Diabetes

20.5.1. Insulins

Insulin, Intermediate Acting (NPH)

ATC code: A10AC

Injection, 100 IU/mL in 10-mL vial (as compound insulin zinc suspension or isophane insulin), LOU 4

Indications and dose

Adult

Diabetes mellitus, by SC injection: According to individual requirements

Paediatric

Diabetes mellitus, SC

Infant or **child:** According to requirements; given in combination with short-acting insulin in which 30% of total daily dose is given as a single evening injection of intermediate-acting insulint; total daily dose initiated at 0.5units/kg/day

Contraindications: IV administration. Hypoglycaemia

Precautions: Acute trauma or illness: insulin requirement may increase.

Surgery: monitor blood glucose and urine ketones perioperatively, soluble insulin infusion may be required in complex or prolonged surgery.

Hepatic impairment: Insulin requirements may be diminished due to reduced insulin metabolism and reduced capacity for gluconeogenesis. Lower initial dosages may be appropriate, with careful monitoring of plasma glucose levels and dosing adjustments.

Renal impairment: May need dose reduction, insulin requirements fall, compensatory response to hypoglycaemia is impaired.

Pregnancy: Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimester. Dose adjustment may be required

Breastfeeding: Dose adjustment may be required

Adverse effects: Common Hypoglycaemia, weight gain. hypoglycaemia in overdose, rarely hypersensitivity reactions, including urticaria and rash, local reactions and lipoatrophy at injection site.

Allergic reactions, local reactions including erythema, itching, lipodystrophy, lipoatrophy.

Interaction with other medicines (*indicates serious):

Refer to Insulin, short acting (soluble)

Notes:

- Cases of cardiac failure reported when pioglitazone is used in combination with insulin
- When given by SC injection, intermediate insulins have an onset of action of approximately 1–2 hours, a maximal effect at 4–12 hours and a duration of 16–35 hours. Some are given twice daily in conjunction with short action (soluble) insulin and others are given once daily. Soluble insulin can be mixed with intermediate insulins.
- Hypoglycaemia, the most frequent and serious adverse effect, may occur with excessive dosage, delayed or insufficient food, increased physical activity. Warning symptoms include sweating, hunger, faintness, palpitations, tremor, headache, visual disturbance and altered mood.
- Patients need to be instructed to rotate the SC injection site to avoid fat necrosis (lipoatrophy) and erratic absorption. Can be a particular problem in children because lipoatrophic area less painful to inject into than normal areas.
- Isophane insulin is a suspension of insulin with protamine, it is of particular value for initiation

of twice daily insulin regimes. Isophane can be mixed with soluble insulin before injection.

» Insulin zinc suspension (30% amorphous, 70% crystalline) has a more prolonged duration of action.

» Refrigerate unopened vials of insulin at 2–8 °C. Once opened vials may be stored in

» refrigerator or at room temperature for up to 28 days.

Insulin, long acting, Detemir

ATC code: A10AE05

Injection, 100IU/ml, 10ml vial, LOU 4

Injection, 100IU/ml, 3ml prefilled pen, LOU 4

Indications and dosage

Adult

Type 1 DM

For insulin naïve, By SC injection: pprox.. 1/3 of individual insulin requirements, of which daily insulin requirements are estimated at 0.1- 0.2units/kg.

The remaining 2/3 of daily insulin dose is used on short acting, premeal insulin.

Type 2 DM

Improve glycaemic control, By SC injection: 10 units or 0.1 – 0.2 units/kg once daily dosage with the evening or divided into a twice daily regimen and titrate accordingly.

Paediatrics

Type 1 DM

Child < 2years: Safety and efficacy not established

Chid 2-17years: By SC injection, pprox.. 1/3 of individual insulin requirements, of which daily insulin requirements are estimated at 0.1- 0.2units/kg. The remaining 2/3 of daily insulin dose is used on short acting, premeal insulin.

Contraindications: During episodes of hypoglycaemia. Hypersensitivity to Insulin detemir or any of the product excipients

Precautions:

Hypokalaemia- Monitor potassium levels in patients at risk of developing hypokalaemia.

Fluid retention and heart failure in patients treated with thiazolidinediones e.g. pioglitazone – monitor for signs of heart failure in patients on both insulin and these medicines.

Elderly – monitor for hypoglycaemia as signs of hypoglycaemia in these patients is generally diminished.

Renal and hepatic impairment: Dose adjustment on an individual basis recommended.

Pregnancy: Maybe acceptable.

Breastfeeding: Safe for use- acceptable.

Adverse effects: Upper respiratory infections, pharyngitis, headache, back pain, influenza-like symptoms, hypokalaemia, hypoglycaemia, lipohypertrophy and lipodystrophy, injection site reactions.

Interactions with other medicine (*serious)
Medicines that may reduce the patient's insulin requirements:*Oral antidiabetic agents, *GLP-1 receptor agonists, monoamine oxidase inhibitors (MAOI), beta-blockers, ACEIs, and sulphonamides.

Medicines that may increase the patient's insulin requirements:

*Oral contraceptives, *diuretics, *corticosteroids, thyroid hormones, *atypical antipsychotics, growth hormone and danazol.

*Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

*Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

Notes

» To be administered subcutaneously into the abdominal area, thigh, or deltoid, and rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy. Do not inject into areas of lipodystrophy.

» Do not administer detemir intravenously or intramuscularly. The intended duration of activity of detemir is dependent on injection into subcutaneous tissue. Intravenous or intramuscular administration of the usual subcutaneous dose could result in severe hypoglycaemia.

» Do not dilute or mix insulin detemir with any other insulin or solution.

» Not recommended for the treatment of diabetic ketoacidosis.

Insulin, Long acting (basal), Glargine

ATC code: A10AE04

Injection, 100 IU/ml, 10ml vial, LOU 4

Injection, 100 IU/ml, 3ml pre-filled pen, LOU 4

Indications and dosage

Adult

Type 1 DM

Improve glycaemic control

For insulin naïve patients. By SC injection: approx. 1/3 of individual insulin requirements, of which daily insulin requirements are estimated at 0.2-0.4units/kg.

The remaining 2/3 of daily insulin dose is used on short acting, premeal insulin.

Type 2 DM

For insulin naïve patients, By SC injection: 0.2 units/kg or up to 10 units once daily.

Paediatrics

Type 1 DM

Children < 2yrs

Safety and efficacy not established

Child 2-17years

By SC injection, pprox.. 1/3 of individual insulin requirements, of which daily insulin requirements are estimated between 1-2 units/kg

Contraindications: During episodes of hypoglycaemia. Hypersensitivity to Insulin glargine or any of the product excipients. **Precautions**

Hypokalaemia- Monitor potassium levels in patients at risk of developing hypokalaemia.

Fluid retention and heart failure in patients treated with thiazolidinediones e.g. pioglitazone – monitor for signs of heart failure in patients on both insulin and these medicines.

Elderly – monitor for hypoglycaemia as signs of hypoglycaemia in these patients is generally diminished.

Renal impairment: May need to decrease dose- due to diminished insulin due to reduced insulin metabolism.

Hepatic impairment: Insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism- need for dose adjustment.

Pregnancy: Maybe acceptable- no data to report a clear association of insulin glargine with birth defects.

Breastfeeding: Acceptable.

Adverse effects: Lipodystrophy, lipohypertrophy, hypokalaemia, hypoglycaemia, influenza-like symptoms, pharyngitis, diarrhoea

Interactions with other medicines (*serious)*Antidiabetic agents, *ACEIs, *ARBs, *fluoxetine, *olanzapine, *corticosteroids, *diuretics, oral contraceptives, beta-blockers

Notes

- To be administered subcutaneously once daily at any time of day but at the same time every day.
- To be administered subcutaneously into the abdominal area, thigh, or deltoid, and rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy. Do not inject into areas of lipodystrophy.
- Individualize and adjust the dosage of glargine based on the individual's metabolic needs, blood glucose monitoring results and glycaemic control goal.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns, during acute illness, or changes in renal or hepatic function.
- Switching of patients from one brand to another should be done under close medical supervision, as changes in strength, manufacturer, type, origin and or method of manufacture may result in need for change in dose
- Inadequate dosing or discontinuation of treatment especially in Type 1 diabetes may lead to hyperglycaemia and diabetic ketoacidosis
- Must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.
- Should not be administered intravenously. The prolonged duration of action of insulin glargine is dependent on its injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.

Insulin, Premixed (Short Acting + Intermediate Acting)

ATC code: A10AD

Injection, 100 IU/mL (10-mL vial), LOU 4

Indications and dose

Adult

Diabetes mellitus, by SC injection: According to individual requirements, administered at or near meals. Individual insulin requirement ranges at 0.3 to 1 IU/kg/day, adjusted according to physical activity, diet, or concomitant illness.

Paediatric

Diabetes mellitus, SC injection

Child over 10 years: According to requirements; administered at or near meals. Individual insulin requirement ranges at 0.3–1 IU/kg/day, adjusted according to physical activity, diet, or concomitant illness.

Contraindication: Hypersensitivity, do not administer intravenously can cause severe hypoglycaemia

Precautions: Hypoglycaemia, risk of cardiac heart failure in patients on combination therapy with thiazolidinedione,

Hepatic impairment: Insulin requirements may be diminished due to reduced insulin metabolism and reduced capacity for gluconeogenesis. Lower initial dosages may be appropriate, with careful monitoring of plasma glucose levels and dosing adjustments.

Renal Impairment: May need dose reduction, insulin requirements fall, compensatory response to hypoglycaemia is impaired

Pregnancy: Intensified blood glucose control and monitoring is recommended throughout pregnancy and when contemplating pregnancy.

Breastfeeding: No restrictions on treatment as it presents no risk to the baby

Adverse effects: Hypogylcaemia, urticaria, rash, eruptions, anaphylactic reactions, painful peripheral neuropathy, refraction disorders, diabetic retinopathy, lipodystrophy, oedema.

Interaction with other medicines:

Refer to Insulin, short acting (soluble).

Notes:

- An injection should be followed within 30 minutes by a meal or carbohydrate containing

snack

- Patients whose blood glucose is greatly improved (e.g. by intensified insulin therapy) may experience change in usual warning symptoms of hypoglycaemia and should be advised accordingly.
- Rapid onset of action should be considered in patients, where delayed absorption of food is expected
- Switching of patients from one brand to another should be done under close medical supervision, as changes in strength, manufacturer, type, origin and or method of manufacture may result in need for change in dose
- Rotate the injection sites to reduce risk of injection site reactions
- Insulin administration may cause insulin antibodies to form, which will necessitate adjustment of dose to correct tendency to hyper- or hypoglycaemia
- In pregnancy, insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimester. After delivery the requirements return to pre-pregnancy levels.
- Inadequate dosing or discontinuation of treatment especially in Type 1 diabetes may lead to hyperglycaemia and diabetic ketoacidosis

Insulin, Premixed (Ultra Short Acting + Intermediate Acting)

ATC code: A10AD

Injection, 100 IU/mL (10-mL vial), LOU 4

Indications and dose

Adult

Diabetes mellitus, by SC injection: According to individual requirements

Paediatric

Diabetes mellitus, by SC injection

Child: According to requirements

Contraindication: IV administration. Hypoglycaemia

Precautions: Hypoglycaemia, risk of cardiac heart failure in patients on combination therapy with thiazolidinedione.

Hepatic impairment: Insulin requirements may be diminished due to reduced insulin metabolism and reduced capacity for gluconeogenesis. Lower initial dosages may be appropriate, with careful monitoring of plasma glucose levels and dosing adjustments.

Renal Impairment: May need dose reduction, insulin requirements fall, compensatory response to hypoglycaemia is impaired

Pregnancy: Data on a large number of exposed pregnancies do not indicate any adverse effect of insulin lispro on pregnancy or on the health of the foetus/newborn.

Breastfeeding: Patients with diabetes who are breastfeeding may require adjustments in insulin dose, diet or both

Adverse effects: Refer to Insulin, short acting (soluble).

Interaction with other medicines:

Refer to Insulin, short acting (soluble).

Notes:

- Patients with pre-existing or gestational diabetes should maintain good metabolic control throughout pregnancy to prevent adverse outcomes associated with hyperglycemia.

Insulin, Short-Acting (Soluble)

ATC code: A10AB

Injection, 100 IU/mL in 10-mL vial, LOU 4

Indications and dose

Adult

Diabetes mellitus, diabetic emergencies and at surgery, diabetic ketoacidosis or coma, hyperglycaemia

Dose according to individual requirements

Paediatric

Diabetes mellitus, SC

Neonate, infant or **child:** According to requirements; used in combination with intermediate- or long-acting insulin in which the total daily dose is initiated at 0.5 units/kg/day; give 70% of the total daily dose as short-acting insulin divided up between 3–4 pre-meal boluses (when given in combination with intermediate-acting insulin); when given in combination with long-acting insulin, 60% of the total daily dose as short-acting insulin divided up between 3–4 pre-meal boluses

Diabetic ketoacidosis or coma, IV infusion

Infant or **child:** 0.05–0.1 units/kg/hour (maximum 0.2 units/kg/hour), depending on the rate of reduction of serum glucose (decreasing the serum glucose level too rapidly may lead to cerebral oedema), until acidosis is corrected and patient is resumed on SC insulin

Precautions: Acute trauma or illness: insulin requirements may increase. Surgery: monitor blood glucose and urine ketones preoperatively, insulin infusion may be required in complex or prolonged surgery.

Hepatic impairment: Insulin requirements may be diminished due to reduced insulin metabolism and reduced capacity for gluconeogenesis. Lower initial dosages may be appropriate, with careful monitoring of plasma glucose levels and dosing adjustments.

Renal impairment: May need dose reduction, insulin requirements fall, compensatory response to hypoglycaemia is impaired.

Adverse effects: Common Hypoglycaemia, weight gain, hypokalaemia when given without potassium in the treatment of diabetic ketoacidosis.

Transient oedema, hypoglycaemia in overdose, rarely hypersensitivity reactions including urticaria and rash,

local reactions and lipoatrophy at injection site.

Allergic reactions, local reactions including erythema, itching, lipodystrophy, lipoatrophy.

Interaction with other medicines (*indicates serious):

Dexamethasone: antagonism of hypoglycaemic effect.

Enalapril: hypoglycaemic effect possibly enhanced.

Ethanol: enhanced hypoglycaemic effect.

Furosemide: antagonism of hypoglycaemic effect.

Hydrochlorothiazide: antagonism of hypoglycaemic effect.

Hydrocortisone: antagonism of hypoglycaemic effect.

Prednisolone: antagonism of hypoglycaemic effect.

Propranolol: enhanced hypoglycaemic effect, propranolol may mask warning signs of hypoglycaemia such as tremor.

Notes:

- *Directions for administration:* Short-acting insulins can be given by SC injection, or by IM injection, or by IV injection, or *By IV infusion*
- *For Continuous SC infusion* using a portable infusion pump. This device delivers a continuous insulin infusion and is patient-activated. It is ideal for patients who suffer recurrent hypoglycemia or marked morning rise in blood-glucose concentration despite optimized multiple-injection regimens. Patients on SC insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced health care team. Some insulin preparations are not recommended for use in SC insulin infusion pumps—may precipitate in catheter or needle—consult product literature.
- *For IV infusion* give continuously in sodium chloride 0.9%. Adsorbed to some extent by plastic infusion set, ensure insulin is not injected into 'dead space' of injection port of the infusion bag.
- For maintenance regimes it is usual to inject 15–30 minutes before meals.
- When injected subcutaneously, soluble insulin has a rapid onset of action (30–60 minutes), a peak action between 2 and 4 hours, and a duration of action of up to 8 hours.
- When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes and its effect disappears within 30 minutes.
- If changing from IV to SC insulin, do not stop the IV infusion until 30–60 minutes after the SC dose (to allow time for effect).
- Administration for IV infusion, dilute to a concentration of 1 unit/mL, with sodium chloride 0.9% and mix thoroughly, insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.
- Hypoglycaemia: The most frequent and serious adverse effect of insulin therapy, may occur with excessive dosage, delayed or insufficient food, increased physical activity. Warning symptoms include sweating, hunger, faintness, palpitations, tremor, headache, visual disturbance and altered mood.
- Patients need to be instructed to rotate the SC injection site to avoid fat necrosis (lipoatrophy) and erratic absorption. Can be a particular problem in children because lipoatrophic area less painful to inject into than normal areas.
- Refrigerate unopened vials of insulin at 2–8 °C. Once opened vials may be stored in refrigerator or at room temperature for up to 28 days. Only use soluble insulin if it is clear and not cloudy.

Insulin, Ultra-Short-Acting (Rapid)

ATC code: A10AB04 (insulin lispro), A10AB05 (insulin aspart), A10AB06 (insulin glulisine)

Injection, 100 IU/mL (10-mL vial), LOU 4

Insulin aspart, insulin glulisine, and insulin lispro are used for initial stabilization of diabetes mellitus. Rapid-acting insulins have a faster onset of action (within 15 minutes) and shorter duration of action (approximately 2–5 hours) than soluble insulin and are usually given by SC injection. For maintenance regimens, these insulins should ideally be injected immediately before meals. Often used in combination with intermediate or long-acting insulin.

Indications and dose

Diabetes mellitus, diabetic ketoacidosis, diabetes during surgery

Adult

According to requirements, total daily requirements vary from 0.5–1 unit/kg/day

Starting doses are often low and titrated based on individual patient insulin requirements. During intensification of insulin therapy it is used in combination with basal insulin, where 50% of total daily dose is calculated at 0.3–0.5 units/kg and given in 3 pre-meal doses.

Paediatric

Diabetes mellitus

Child 1 to 17 years: Dosing is according to individual insulin requirements. Initiate treatment by calculating total daily dose of 0.5–0.75 units/kg/day; give 60% of total daily dose in 3–4 pre-meal boluses. Used in combination with long acting insulin.

Diabetic ketoacidosis (DKA), IV infusion:

Child 1 to 17 years: 0.05 units/kg/hour to 0.1 units/kg/hour

Once DKA is resolved, switch to SC insulin;

for prepubertal age: dose at 0.5–1 unit/kg/day

for pubertal age: dose at 1–2 units/kg/day,

overlapped with intermediate or long-acting insulin at 0.3 units/kg with IV insulin for 2 hours

Hyperglycaemic hyperosmolar state (HHS)

Child 1 to 17 years: 0.025–0.05 units/kg/hour via infusion pump

Once HHS resolved, switch to SC insulin; for **prepubertal** age dose at 0.5–1 unit/kg/day for **pubertal** age dose at 1–2 units/kg/day, overlapped with intermediate or long-acting insulin at 0.3 units/kg with IV insulin for 2 hours.

Hepatic impairment: Insulin requirements may be reduced in patients with hepatic impairment due to reduced capacity for gluconeogenesis and reduced insulin breakdown, however, in patients with chronic hepatic impairment, an increase in insulin resistance may lead to increased insulin requirements.

Renal impairment: Insulin requirements may be reduced in the presence of renal impairment

Pregnancy: Dose adjustment may be required during pregnancy and after delivery

Breastfeeding: No restrictions on use, the dose may need to be adjusted however there no reported risk to the baby.

Adverse effects: Hypoglycemia, Hypokalemia, and Skin changes at injection site (lipoatrophy or lipohypertrophy)

Rare adverse effects (often transient and occur when there is rapid improvement of blood glucose levels) include: Refraction disorder, Swollen joints, Diabetic neuropathy and Local allergic reactions at site of injection

Interaction with other medicines (*indicates serious):

Octreotide can increase risk of either hypoglycaemia or hyperglycaemia

Increased risk of hypoglycaemia when taken together with:

Anabolic steroids (e.g. testosterone), ACEIs, *Beta-blockers, MAOIs (e.g., Selegiline),

Other antidiabetic agents (e.g., *Pioglitazone), Salicylates, Sulphonamides

Increased risk of hyperglycaemia when taken together with:

Danazol, Glucocorticoids (e.g., cortisone), Growth hormone, Oral contraceptives, Sympathomimetics (e.g. epinephrine, or salbutamol, terbutaline), Thiazides, Thyroid hormones (levothyroxine)

Notes:

- Rapid-acting insulin, administered before meals, has an advantage over short-acting soluble insulin in terms of improved glucose control, reduction of HbA1c, and reduction in the incidence of severe hypoglycaemia, including nocturnal hypoglycaemia
- When necessary, insulin lispro can be given soon after meals.
- The routine use of post-meal injections of rapid-acting insulin should be avoided—when given during or after meals, they are associated with poorer glucose control, an increased risk of high postprandial-glucose concentration, and subsequent hypoglycaemia.
- Directions for administration**:** Rapid-acting injectable insulins can be given by: SC injection, or by IM injection, or by IV injection, or *By IV infusion*
- Rapid acting insulins are available as vials or prefilled pens- Pens in use should not be stored in refrigerator
- Directions on how to use various insulin pen devices are available with product package leaflet
- In use pens can be stored for 4 weeks at under 25°C, away from direct heat and light
- Store vials and pens not in use at 2-8°C

20.5.2. Oral Hypoglycaemic Agents

20.5.2.1. Sulphonylureas

Gliclazide

ATC code: A10BB09

Tablet (m/r), 30 mg, 60mg, LOU, 3

Tablet (i/r), 40 mg, 80mg, LOU, 3

Indications and dose

Adult

Type 2 diabetes mellitus (non-insulin-dependent), when diet and exercise do not result in adequate glycemic control:

- Initially 30 mg gliclazide m/r once daily, adjusted according to response up to 120 mg once daily in successive steps (30 mg, 60 mg, 90 mg, 120 mg) OR
- Initially, 40–80 mg gliclazide IR daily, adjusted according to response, up to 160 mg as a single dose, with breakfast, higher doses divided, max. 320 mg daily

Paediatric

No or insufficient experience in children and adolescents, therefore its use is not recommended

Contraindications: It is contraindicated in the presence of ketoacidosis. Avoided where possible in acute porphyria. Contraindicated combination-miconazole, alcohol,

Hepatic impairment: Avoid use in hepatic impairment -hypoglycaemic episode occurring in these patients may be prolonged

Renal impairment: In patients with mild to moderate renal insufficiency the same dosing regimen can be used as in patients with normal renal function with careful patient monitoring. Avoid use in severe renal impairment -hypoglycaemic episode occurring in these patients may be prolonged.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended**.**

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Hypoglycaemia, GI disturbances such as nausea, vomiting, diarrhoea, and constipation

Rarely reported adverse effects: *Steven Johnson Syndrome,*Toxic Epidermal Necrolysis drug rash with eosinophilia and systemic symptoms, *Cholestatic jaundice, transient visual disturbances

Interaction with other medicines (*indicates serious):

Increased risk of hypoglycaemia when taken together with: Other antidiabetic agents (insulins, biguanides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists), ACEIs (e.g., captopril, enalapril), testosterone, anabolic steroids, beta-blockers, fluconazole, H2-receptor antagonists, MAOIs, trimethoprim, sulfonamides, clarithromycin, octreotide and NSAIMs

Increased risk of hyperglycaemia when taken together with: *danazol, *chlorpromazine, *glucocorticoids, salbutamol, terbutaline, St. John's wart

Combinations to use with precaution: Fluroquionolones and anticoagulants

Gliclazide effect reduced by Rifamycins, phenothiazines, corticosteroids, loop and thiazide diuretics, diazoxide, oestrogens, progesterones and oral contraceptives

Voriconazole

Notes:

- Recommended to swallow the dose without crushing or chewing
- May encourage weight gain and should be prescribed only if poor control and symptoms persist despite adequate attempts at dieting
- For patients at high risk of hypoglycaemia the minimum dose of 30 mg is to be used.
- When switching from i/r to m/r tablet, gliclazide 80 mg (i/r) is equivalent to gliclazide 30 mg m/r
- It is recommended that oral hypoglycaemic therapy is changed to insulin before pregnancy is attempted and as soon as it is discovered.

20.5.2.2. Biguanides

Metformin

ATC code: A10BA02

Tablet, 500 mg, 850 mg, 1 g (as HCl), LOU 3 (for paediatric LOU 4)

Indications and dose

Adult

Type 2 diabetes mellitus (non-insulin-dependent): 500 mg every 8 hours with or after food (maximum 2 g daily in divided doses)

Type 2 diabetes mellitus (non-insulin-dependent) and CKD

- eGFR <30 mL/min: Discontinue metformin
- eGFR 30 to 44 mL/min: Maximum dose is 1000 mg/day

Paediatric

Type 2 diabetes mellitus (non-insulin-dependent), oral

Child 8–10 years: Initially 200 mg once daily adjusted according to response at intervals of at least a week; maximum 2 g daily in 2–3 divided doses

Child over 10 years: Initially 500 mg once daily adjusted according to response at intervals of at least a week; maximum 2 g daily in 2–3 divided doses

Contraindications: Acidosis, including diabetic ketoacidosis, use of iodine-containing X-ray contrast media, general anaesthesia, severe renal impairment (withdraw if renal impairment suspected), hepatic impairment, heart failure, severe infections or trauma, dehydration, alcohol dependence, pregnancy.

Precautions: substitute with insulin during severe infection, trauma, surgery, dehydration breastfeeding.

Hepatic impairment: Avoid use in hepatic impairment, risk of lactic acidosis.

Renal impairment: Metformin should be used cautiously in renal impairment because of the increased risk of lactic acidosis, it is contraindicated in children with significant renal impairment. To reduce the risk of lactic acidosis, metformin should be stopped or temporarily withdrawn in those at risk of tissue hypoxia or sudden deterioration in renal function, such as those with dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure or hepatic impairment. Determine renal function before treatment and once or twice annually

Adverse effects: anorexia, nausea and vomiting, diarrhea patients with renal failure (discontinue), decreased vitamin B12 absorption.

Malabsorption of vitamin B12, nausea, vomiting, anorexia, diarrhoea.

Rash.

Rare: Lactic acidosis (see below), acute hepatitis, hypoglycaemia.

Lactic acidosis, which is rare, but often fatal, may be associated with metformin accumulation when precautions or high-risk situations are overlooked. Early symptoms include anorexia, nausea, vomiting, abdominal pain, cramps, malaise and weight loss.

Interaction with other medicines: alcohol, cimetidine and other cationic medication excreted by renal tubular transport (such as: amiloride, nifedipine, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin), Furosemide, vitamin B12.

Dexamethasone: antagonism of hypoglycaemic effect.

Enalapril: hypoglycaemic effect possibly enhanced.

Ethanol: enhanced hypoglycaemic effect, increased risk of lactic acidosis.

Furosemide: antagonism of hypoglycaemic effect.

Hydrochlorothiazide: antagonism of hypoglycaemic effect.

Hydrocortisone: antagonism of hypoglycaemic effect.

Prednisolone: antagonism of hypoglycaemic effect.

Propranolol: propranolol may mask warning signs of hypoglycaemia such as tremor.

Notes:

» Doses should be administered with a meal. GI adverse effects are initially common with metformin, and may persist in some children, particularly when high doses are given. A slow increase in dose may improve tolerability.

20.5.2.3. Thiazolidinediones

Pioglitazone

ATC code: A10BG03

Tablet, 15 mg, 30mg, LOU 4

Indications and dose

Type 2 diabetes mellitus

» Monotherapy: Adjunct to diet and exercise to improve glycemic control

» Combination therapy: With sulfonylurea, metformin, or insulin, when diet, exercise, and a single agent alone do not result in adequate glycemic control

Adult

» *Monotherapy:*

» Initial 15–30 mg once daily

» If response is inadequate, dosage may be increased in increments up to 45 mg once daily

» Maximum recommended dose 45 mg once daily

Combination therapy:

» Maximum recommended dose 45 mg/day

» With sulphonylureas: Initial 15–30 mg once daily

» With metformin: Initial 15–30 mg once daily

» With insulin: Initial 15–30 mg once daily

Paediatric

No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: hypersensitivity reaction, active liver disease, patients who have experienced jaundice during therapy, cardiac failure or history of cardiac failure (New York Heart Association stages I to IV), diabetic ketoacidosis, current bladder cancer or a history of bladder cancer and uninvestigated macroscopic haematuria

Precautions: Use in type 1 diabetes is not recommended, anemia

Hepatic impairment: Avoid use in hepatic impairment

Renal Impairment: No dosage adjustment is necessary in patients with impaired renal function. No information is available from dialyzed patients therefore pioglitazone should not be used in such patients.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: serum triglycerides decreased, HDL-cholesterol increased, weight gain, upper respiratory tract infection, edema, headache, fatigue, hypoglycemia, anemia, myalgia, sinusitis, pharyngitis, anaemia, hypo-aesthesia, visual disturbance, heart failure, increased risk of bone fracture, haematuria, erectile dysfunction. adverse effects include: bladder cancer, insomnia

Interaction with other medicines (*indicates serious):

*CYP2C8 Inhibitors: may increase serum concentration of pioglitazone.

delavirdine, fluconazole, ketoconazole, NSAIMs, sulfonamides, amiodarone, fluoxetin, glimepride, glipizide, phenytoin, sertraline, warfarin, St. John's Wort.

Notes:

» No dosage adjustment is necessary for elderly patients, start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin

» Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure

20.5.2.4. Dipeptidylpeptidase (DPP)-4 inhibitors (Gliptins)

Linagliptin

ATC codes : A010BH05

Tablet, 5mg, LOU 5

Indications and dosage

Adults

Type 2 DM as monotherapy or in combination with other antidiabetic agents, 5mg once daily

Paediatrics

Safety and efficacy not established.

Contraindications: Hypersensitivity to the active ingredient or to any of the excipients in the product.

Precautions: History of pancreatitis.

Renal and hepatic impairment: No dose adjustment required.

Pregnancy: Avoid use.

Breastfeeding: Avoid use.

Adverse effects: Hypoglycaemia, nasopharyngitis, hyperlipidemia, weight gain, cough, angioedema, acute pancreatitis, rash, mouth ulceration

Interactions with other medicines (*serious): Rifampicin, protease inhibitors, phenobarbital, carbamazepine, clobazam, phenytoin.

Notes

» Should not be used on type 1 DM.

Sitagliptin

ATC code: A10BH01

Tablets, 50 mg, 100mg, LOU 4

Indications and dose

Type 2 diabetes mellitus

- Monotherapy
- Combination therapy with metformin, sulfonylurea (gliclazide), thiazolidinedione (pioglitazone), or insulin

Adult

- Monotherapy: 100 mg once daily
- Combination therapy:
  - When used with metformin and/or thiazolidinedione, the dose of metformin and/or thiazolidinedione should be maintained, and sitagliptin administered concomitantly
  - When sitagliptin is used in combination with a sulphonylurea or insulin, a lower dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia

Paediatric

No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Hypersensitivity

Precautions: Should not be used in treatment of Type 1 diabetes mellitus, diabetes ketoacidosis**.** Associated with increased risk of developing acute pancreatitis

Hepatic impairment: No dose adjustment is necessary for patients with mild to moderate hepatic impairment. Since it is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin, however care should be exercised.

Renal Impairment: When considering the use of sitagliptin in combination with another anti-diabetic agents, its conditions for use in patients with renal impairment should be checked.

For patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60 to < 90 mL/min), no dose adjustment is required.

For patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min), no dosage adjustment is required.

For patients with moderate renal impairment (GFR ≥ 30 to < 45 mL/min), the dose of sitagliptin is 50 mg once daily.

For patients with severe renal impairment (GFR ≥ 15 to <30 mL/min) or with ESRD (GFR < 15 mL/min), including those requiring haemodialysis or peritoneal dialysis, the dose of sitagliptin is 25 mg once daily. Treatment may be administered without regard to the timing of dialysis

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Hypoglycemia, acute pancreatitis, acute kidney injury, bundle branch block, exfoliative dermatitis. May develop arthralgia, bullous pemphigoid, pancreatitis, hypersensitivity reactions.

Interaction with other medicines: No serious interactions known

Notes:

- If a dose of is missed, it should be taken as soon as the patient remembers, a double dose should not be taken on the same day.
- As dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of sitagliptin and periodically thereafter

20.5.2.5. Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors

Empagliflozin

ATC code: A10BK03

Tablet, 10 mg, LOU 4

Tablet, 25 mg, LOU 5

Indications and dose

Adult

Type 2 diabetes mellitus as monotherapy or in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control), over 18 years of age and less than 85 years: 10 mg once daily, increased to 25 mg once daily if necessary and if tolerated

- **Elderly:** 85 years and over: Not recommended

Type 2 diabetes mellitus in patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 mL/min/1.73 m2 and need tighter glycaemic control: Dose can be increased to 25 mg once daily; maximum daily dose 25 mg

Paediatric

No or insufficient experience in children and adolescents, therefore its use is not recommended.

Contraindications: Diabetic ketoacidosis, dialysis, increased risk of bone fracture

Precautions: Complicated urinary tract infections—consider temporarily interrupting treatment. Risk of volume depletion in the elderly- consider interrupting treatment if volume depletion occurs, surgical procedures. Limited experience with use in patients with heart failure, hypotension.

Hepatic Impairment: No dosage adjustment required

Renal Impairment: Empagliflozin can be initiated at eGFR of ≥30 mL/min/1.73 m2. There may be an initial decline in eGFR after therapy is initiated but if there is a sustained decline, the clinician may consider stopping the drug. Thus, the cut-off for empagliflozin below which it should not be initiated is a GFR of <30 mL/min/1.73 m2.

Pregnancy: No or insufficient data on the effects of the drug on the foetus and/or mother during pregnancy

therefore its use is not recommended.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Common or very common: Balanoposthitis, hypoglycaemia (in combination with insulin or sulfonylurea), increased risk of infection, skin reactions, thirst, constipation, urinary tract infections (pyelonephritis and urosepsis), increased urination, increased serum lipids and volume depletion, Hypovolaemia

*Diabetic ketoacidosis, angioedema,
*Fournier's gangrene

Interaction with other medicines (*indicates serious):

*Insulins: Sodium-glucose cotransporter 2 (SGLT2) inhibitors may enhance the hypoglycemic effect of Insulins.

*Sulfonylureas: SGLT2 inhibitors may enhance the hypoglycemic effect of sulfonylureas

Loop diuretics: Empagliflozin may enhance the hypotensive effect of Loop Diuretics

Quinolones: May enhance the hypoglycemic effect of agents with blood glucose lowering effects.

Salicylates: May enhance the hypoglycemic effect of Agents with blood glucose lowering effects.

Thiazide and thiazide-like diuretics: May diminish the therapeutic effect of antidiabetic agents.

Androgens: May enhance the hypoglycemic effect of agents with blood glucose lowering effects.

Notes:

- When empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.
- Monitoring requirements -determine renal function before treatment and before initiation of concomitant drugs that may reduce renal function, then at least annually thereafter.
- Patient and Caregiver advice- Patients should be informed of the signs and symptoms of diabetic ketoacidosis

20.5.2.6. Fixed Dose Combination-Oral Hypoglycaemic Agents

Empagliflozin + Metformin

ATC Code : A10BD20

Tablet, 5mg+500mg, LOU 4

Tablet, 5mg+1000mg, LOU 4

Tablet, 12.5mg+500mg, LOU 4

Tablet, 12.5mg+1000mg, LOU 4

Indications and dosage

Adult

Type 2 DM Adjunct combination therapy to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).

Patients on metformin: switch to empagliflozin 10 mg / day with a similar total daily dose of metformin

Patients on empagliflozin: switch to metformin 1000 mg/ day with a same total daily dose of empagliflozin

Patients already treated with empagliflozin and metformin: switch to same total daily doses of each component (or nearest appropriate dose of metformin)

For additional glycemic control, empagliflozin may be increased to maximum total daily dose of 25 mg in patients tolerating 10 mg/day and metformin may be increased to maximum total daily dose of 2,000 mg/ day, with gradual escalation to reduce gastrointestinal adverse reactions with metformin.

Paediatrics

Child< 18years: safety and efficacy not established.

Contraindications: *(Refer to individual monographs)*

Precautions: *(Refer to individual monographs)*

Renal and hepatic impairment: *(Refer to individual monographs)*

Pregnancy and breastfeeding: *(Refer to individual monographs)*

Adverse effects: *(Refer to individual monographs)*

Interactions with other medicines: *(Refer to individual monographs)*

Pioglitazone + metformin

ATC code : A10BD05

Tablet, 15+500mg, LOU 4

Tablet,15+850mg, LOU 4

Indications and dosage

Adult

Type 2 DM not controlled by metformin alone: 1 tablet twice daily, titration with the individual components (pioglitazone and metformin) desirable before initiation

Paediatrics: Not used- safety and efficacy not established

Contraindications: *(Refer to individual monographs)*
Precautions: *(Refer to individual monographs)*

Renal and hepatic impairment: *(Refer to individual monographs)*

Pregnancy and breastfeeding: *(Refer to individual monographs)*

Adverse effects: *(Refer to individual monographs)*

Interaction with other medicines: *(Refer to individual monographs)*

Sitagliptin + Metformin

ATC code : A10BD07

Tablets, 50mg+500mg, LOU 4

Tablet, 50mg+850mg, LOU 4

Tablet, 50mg+1000mg, LOU 4

Indications and dosage

Adults

Type 2 DM

Adjunct in patients inadequately controlled on their maximal tolerated dose of metformin alone or combination of sitagliptin and metformin or metformin and a sulphonylurea or metformin and a PPARγ agonist (i.e., a thiazolidinedione) or insulin and metformin.

Not currently on metformin: 50mg sitagliptin/500mg metformin twice daily

Currently on metformin: 50mg twice daily of sitagliptin (100 mg total daily dose) and current daily dose of metformin

Paediatrics

Safety in children and adolescents <17years not established.

Contraindications: Refer to individual monographs)

Precautions

Dosing in renal and hepatic impairment

Adverse reactions: (refer to individual monographs)

Interactions with other medicines: (refer to individual monographs)

Notes:

- The dose of antihyperglycaemic therapy with sitagliptin/metformin hydrochloride should be individualised based on patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin.
- When sitagliptin/metformin hydrochloride is used in combination with a sulphonylurea or insulin, a lower dose of the sulphonylurea and insulin may be required to reduce the risk of hypoglycaemia.
- For the different doses on metformin, sitagliptin/metformin hydrochloride is available in strengths of 50 mg sitagliptin and 850 mg metformin hydrochloride or 1,000 mg metformin hydrochloride.

20.6. Medicines For Hypoglycaemia

Diazoxide

ATC code: V03AH01

Suspension, 50 mg/mL, LOU 4

Indications and dose

Diazoxide may be used pre-operatively as temporary measure and post-operatively if hypoglycaemia persists.

Adult

Hypoglycaemia due to hyperinsulinism associated with Inoperable islet cell adenoma or carcinoma or extra pancreatic malignancy, oral

5 mg/kg divided into 2 or 3 doses per 24 hours; this can be increased based on the patient's response until the symptoms and blood glucose level respond satisfactorily. Usual maintenance dose is 3–8 mg/kg/day given in 2–3 divided doses.

Paediatric

Hypoglycaemia due to hyperinsulinism associated with Leucine sensitivity, islet cell hyperplasia, nesidioblastosis, extra pancreatic malignancy, islet cell adenoma, or adenomatosis, oral:

Neonate: Initially 5 mg/kg twice daily, adjusted according to response; initial dose used to establish response; maintenance 1.5–3 mg/kg 2–3 times a day, increase if necessary up to 7 mg/kg 3 times a day; higher doses are unlikely to be beneficial, but may be required in some cases

Child: Initially 1.7 mg/kg 3 times a day, adjusted according to response; maintenance 1.5–3 mg/kg 2–3 times a day; increase if necessary up to 5 mg/kg 3 times a day, doses up to 5 mg/kg may be required in some cases, but higher doses unlikely to be beneficial

Contraindication: hypersensitivity to diazoxide or other thiazides. Contraindicated in functional hypoglycaemia.

Precautions: Treatment initiation should be under close clinical supervision, discontinue if not effective in 2–3 weeks. Use with caution in patients with aortic coarctation, aortic stenosis, arterio-venous shunt, heart failure, hyperuricaemia, impaired cardiac circulation, impaired cerebral circulation

Hepatic Impairment: No or insufficient data on the pharmacokinetics of this drug in hepatic impairment. Therefore, uptitration should be done with caution.

Renal Impairment: Dose reduction may be required

Pregnancy: Pregnancy Category C. Use only if essential, alopecia and hypertrichosis reported in neonates whose mothers received oral diazoxide during last 19–60 days of pregnancy, may inhibit uterine activity during labour. May produce foetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism.

Breastfeeding: No or insufficient data on the amount of drug excreted in breast milk or the effect on the infant therefore its use is not recommended.

Adverse effects: Abdominal pain, albuminuria, appetite decreased (long term use), arrhythmia, azotaemia, cardiomegaly, cataract, constipation, diabetic hyperosmolar coma, diarrhoea, dizziness, dyspnoea, eosinophilia, extrapyramidal symptoms, development of abnormal facial features (in children), fever, fluid retention, galactorrhoea, haemorrhage, headache. heart failure, hirsutism, hyperglycaemia, hyperuricaemia (long term use), hypogammaglobulinaemia, hypotension, ileus, ketoacidosis, leucopenia, libido decreased, musculoskeletal pain, nausea, nephritic syndrome, oculogyric crisis, pancreatitis, parkinsonism, pulmonary hypertension, skin reactions, sodium retention, taste altered, thrombocytopenia, tinnitus, vision disorders, voice alteration (long term use), vomiting

Interaction with other medicines: Chlorpromazine, coumarin anticoagulants, Thiopental, Thiazide-Like Diuretics, Phenytoin, Blood Pressure Lowering Agents

Notes:

- Diazoxide should only be used after diagnosis

of hypoglycaemia due to the conditions listed above is established

- In adults with benign or malignant islet-cell tumors producing large quantities of insulin, high dosages of up to 1000 mg (1 g) daily have been used.
- Antidiuretic property may lead to significant fluid retention, which may precipitate congestive heart failure in patients with compromised cardiac reserve.
- *Monitoring Requirements:* Monitor blood pressure, urinary sugar and ketones, Monitor white cell and platelet count during prolonged use. Regularly assess growth, bone, and psychological development during prolonged use.
- Benzothiazide diuretics may intensify hyperglycaemic and hyperuricemic effects
- Hyperglycaemic effects are intensified in presence of hypokalemia
- Diazoxide is highly bound to serum proteins, may displace other protein bound substances
- Hepato-renal adverse effects include increased SGOT, alkaline phosphatase, decreased CrCl, reversible nephrotic syndrome, decreased urinary output, hematuria, albiminuria
- Overdosage of diazoxide causes marked hyperglycaemia which may be associated with ketoacidosis. It responds to prompt insulin administration and restoration of fluid and electrolyte imbalance. Prolonged surveillance of blood glucose levels required for up to 7 days due to its long half-life (approximately 30 hours)

Glucagon

ATC code : H04AA01

Injection, 1mg/ml, LOU 4

Indications and dosage

Adult

Diabetic hypoglycaemia:

Adult: By SC or IM injection, 1mg, if no response within 10 minutes give dextrose IV. If the patient does not respond within 10 minutes, intravenous glucose should be given

Paediatric

Child 1 month–8 years (body weight up to 25 kg), By SC or IM injection: 500 micrograms, if no response within 10minutes intravenous glucose should be given.

Child 9–17 years (body weight 25 kg and above), By SC or IM injection: 1 mg, if no response within 10minutes intravenous glucose should be given.

Contraindications: Hypersensitivity to the active substance or to any of the excipients

Phaeochromocytoma

Precautions

Glucagonoma

Ineffective in chronic hypoglycaemia, starvation, and adrenal insufficiency and insulinoma.

Renal and hepatic impairment: No dose adjustment required.

Pregnancy: Safe for use.

Breastfeeding: Safe for use.

Adverse effects: Nausea, vomiting, hyperglycaemia, headache, injection site reactions, abdominal pains.

Interactions with other medicines (*serious)
*Anticholinergic drugs (atropine, benztropine, dicyclomine, ipratropium, hyoscine) *Insulin, *warfarin, beta-blockers, *indomethacin

Notes

- 1 unit is equivalent to 1mg of glucagon
- When the patient has responded to the treatment, give oral carbohydrate to restore the liver glycogen and prevent relapse of hypoglycaemia.

20.7. Thyroid Hormones & Anti-Thyroid Medicines

Carbimazole

ATC code: H03BB01

Tablet, 5 mg, 10 mg, LOU 4

Indications and dose

Adult

Hyperthyroidism (first episode in patient <40 years), control thyrotoxicosis in both Grave's disease and toxic nodular goitre, preoperatively to reach euthyroid state, along with radioactive iodine (given after 5 to 7 days and withdrawn till response develops), thyroid storm, oral: 15–40 mg daily in divided doses, until patient becomes euthyroid (usually 4–8 weeks), then reduce to a maintenance dose of 5–15 mg for 12–18 months

Paediatric

Hyperthyroidism, oral:

Neonate: Initially 750 micrograms/kg daily until patient is euthyroid, usually after 8 to 12 weeks, then gradually reduce to a maintenance dose of 30–60% of the initial dose; higher initial doses (up to 1 mg/kg daily) are occasionally required, particularly in thyrotoxic crisis; dose may be given in single or divided doses

Child 1 month–11 years: Initially 750 micrograms/kg daily until patient is euthyroid, usually after 4–8 weeks, then gradually reduce to a maintenance dose of 30–60% of the initial dose; higher initial doses are occasionally required, particularly in thyrotoxic crisis; dose may be given in single or divided doses; maximum 30 mg per day

Child 12–17 years: Initially 30 mg daily until euthyroid, usually after 4–8 weeks, then gradually reduce to a maintenance dose of 30–60% of the initial dose; higher initial doses are occasionally required, particularly in thyrotoxic crisis; dose may be given in single or divided doses

Contraindications/Precautions: Hypersensitivity, pregnancy, breastfeeding, liver disorders

Hepatic impairment: Manufacturer advises use with caution in mild to moderate insufficiency—half-life may be prolonged, avoid in severe insufficiency

Adverse effects: Major Adverse effects- hepatitis, SLE like syndrome. Most serious-agranulocytosis but reversible, hypothyroidism and goitre may occur due to over treatment but is reversible once stopped. GI Intolerance, skin rashes, urticaria, joint pain, loss of hair, loss of taste, fever.

Interaction with other medicines (*indicates serious):

Carbimazole may enhance the anticoagulant effect of vitamin K antagonists.

Antithyroid Agents may increase the serum concentration of Cardiac Glycosides

Antithyroid Agents may increase the serum concentration of Theophylline Derivatives

*Antithyroid Agents may diminish the therapeutic effect of sodium iodide I131

Carbimazole may decrease the serum concentration of PrednisoLONE (Systemic).

*Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical).

Levothyroxine (Thyroxine Sodium, Thyroxine and T4)

ATC code: H03AA01

Tablet, 25 micrograms, 50 micrograms, 100 micrograms (sodium salt), LOU 4

Indications and dose

Adult

Hypothyroidism, oral:

- **Adult 18–49 years:** Initially 50–100 micrograms once daily, adjusted in steps of 25–50 micrograms every 3–4 weeks, adjusted according to response; maintenance 100–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g., coffee, tea), or other medication
- **Adult 50 years and over:** Initially 25 micrograms once daily, adjusted in steps of 25 micrograms every 4 weeks, adjusted according to response; maintenance 50–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g., coffee, tea), or other medication

Hyperthyroidism (blocking-replacement regimen) in combination with carbimazole, oral: **Adult:**50–150 micrograms daily therapy usually given for 18 months

Lugols Iodine Solution

ATC code: D08AG

Solution, Approximately 130 mg of total iodine/mL,

LOU 4

Indications and dose

Adult

Thyrotoxicosis, thyrotoxic crisis: 0.1–0.3 mL 3 times a day

Paediatric

Neonatal thyrotoxicosis, oral

Neonate: 0.05–0.1 mL three times daily

Thyrotoxicosis (preoperative), oral

Neonate: 0.1–0.3 mL three times daily

Infant or **child:** 0.1–0.3 mL three times daily

Thyrotoxic crisis, oral

Infant: 0.2–0.3 mL three times daily

Child: 1 mL three times daily

Contraindications: Breastfeeding (possibly concentrated in milk, risk of neonatal goiter and hypothyroidism), pregnancy (risk of neonatal hypothyroidism), surgery for toxic nodular goitre (may worsen hyperthyroidism), pulmonary oedema, hyperthyroidism, severe renal impairment.

Precautions: Long-term use, cystic fibrosis, myotonia congenita, Addison disease, TB, acute bronchitis, treatment may worsen acne, cardiac disease.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Use with caution.

Adverse effects: Hypersensitivity reactions manifested by angioedema, fever, arthralgia, urticaria, metallic taste, headache, swelling and tenderness of the salivary glands

Common GI intolerance including nausea, vomiting, diarrhoea and metallic taste.

or rare Hypersensitivity reactions, including corzya-like symptoms, headache, lacrimation, conjunctivitis, pain in salivary glands, laryngitis, bronchitis, rashes, on prolonged treatment, insomnia and depression, cardiac arrhythmias.

Interaction with other medicines:

Sodium iodide (iodine-131): decreased effect.

Enalapril: increased effect/toxicity.

Notes:

- Administration: Dilute well with milk or water.
- Lugol's solution: iodine 5%, potassium iodide 10% in freshly boiled and cooled purified water.
- Also known as strong iodine solution.
- Easily confused with potassium iodide.

Propranolol

ATC code: C07AA05

Tablet (scored), 40 mg, LOU 4

Indications and dose

Adult

Thyrotoxicosis, oral: 60–80 mg/day every 6–8 hours OR 30–160 mg/day adjusted for heart rate and blood pressure

Paediatric

Hyperthyroidism/thyrotoxicosis, oral

Neonate: Initially 250–500 micrograms/kg every 6–8 hours, adjusted according to response

Child: Initially 250–500 micrograms/kg every 8 hours, adjusted according to response, increased if necessary up to 1 mg/kg every 8 hours (max. per dose 40 mg every 8 hours)

Contraindications: Hypersensitivity to propranolol, beta blockers, or any component of the formulation, uncompensated congestive heart failure (unless the failure is due to tachyarrhythmias being treated with propranolol), cardiogenic shock, severe sinus bradycardia or heart block greater than first degree (except in patients with a functioning artificial pacemaker), severe hyperactive airway disease (asthma or chronic obstructive pulmonary disease).

Precautions: peripheral arterial insufficiency, first degree atrioventricular block, major surgery, renal and hepatic impairment, diabetes, myasthenia gravis, pregnancy. Avoid abrupt withdrawal.

Hepatic impairment: Increased risk of hepatic encephalopathy due to increased half-life. Consider dose reduction with oral.

Renal impairment: Dose reduction may be required.

Adverse effects: heart failure, heart block, hypotension, bronchospasm, fatigue and coldness of the extremities, headache, depression, dizziness, confusion and sleep disturbances, dry mouth, nausea, vomiting, diarrhea, impotence or decreased libido.

Interaction with other medicines:

chlorpromazine, phenothiazines, thioxanthenes, lidocaine, cimetidine, hepatic enzyme inducers, (barbiturates, phenytoin, rifampicin), non-steroidal anti-inflammatory agents, digoxin, verapamil, neuromuscular blocking agents, anaesthetic agents, insulin or oral antidiabetic agents.

Propylthiouracil

ATC code: H03BA02

Tablet, 50 mg, LOU 4

Indications and dose

Adult

Thyrotoxic crisis/storm, thyrotoxicosis: Loading dose of 500 to 1,000 mg followed by 250 mg every 4 hours

Hyperthyroidism (including Graves disease): Initial 50 to 150 mg (depending on severity) 3 times daily to restore euthyroidism; maintenance dose of 50 mg 2 to 3 times daily for a total of 12 to 18 months, then discontinue if thyroid function tests (e.g., thyroid stimulating hormone (TSH) are normal at that time

Adjust dosage to maintain T3, T4, and TSH in normal range; elevated T3 may be sole indicator of inadequate treatment. Elevated TSH indicates excessive antithyroid treatment.

Paediatric

For all age groups: Adjust as necessary; higher doses occasionally required, particularly in thyrotoxic crisis.

Hyperthyroidism, oral

Neonate: Initially 2.5–5 mg/kg twice daily until euthyroid

Infant: Initially 2.5 mg/kg three times daily until euthyroid

Child 1–5 years: Initially 25 mg three times daily until euthyroid

Child 5–12 years: Initially 50 mg three times daily until euthyroid

Note: Maintenance dosage to maintain euthyroid state is commonly 30–60% of the initial dose.

Hepatic impairment: Rare severe hepatic reactions including hepatic necrosis and hepatitis may occur. Children appear to be at higher risk of propylthiouracil-induced liver injury than adults. Withdraw treatment if hepatic function deteriorates (fatal reactions reported).

Renal impairment: Mild to moderate: use 75% of the normal dose.

Severe: use 50% of the normal dose.

Adverse effects: Occur most often during the first 8 weeks of treatment. Itching and mild rashes may respond to antihistamines while continuing treatment.

Nausea, rash, pruritus, arthralgia, headache, rarely alopecia, cutaneous vasculitis, thrombocytopenia, aplastic anaemia, lupus erythematosus-like syndrome, jaundice, hepatitis, hepatic necrosis, encephalopathy, and nephritis.

Common: Itching, rash, mild leukopenia, nausea, vomiting, gastric discomfort, headache, arthralgia.

Rare: Agranulocytosis, hypoprothrombinemia and bleeding, myositis, hepatotoxicity, vasculitis, lupus-like syndrome.

Agranulocytosis Most likely in first 3 months of treatment, its rapid onset means regular monitoring is of questionable value.

Hepatotoxicity Asymptomatic increases in serum aminotransferases may occur commonly during the first 2 months of propylthiouracil treatment, but resolve with continued treatment. Serious hepatotoxic reactions (usually hepatocellular hepatitis) occur rarely with propylthiouracil and may be immune-based.

Interaction with other medicines (*indicates serious):

Sodium iodide (iodine-131): avoid combination.

* Warfarin: decreased anticoagulant effect.

Notes:

- Patient advice Warn patient or Caregiver to tell doctor immediately if sore throat, mouth ulcers, bruising, fever, malaise or non-specific illness occur.
- Where possible, carbimazole (not on the EML for children) should be used in place of propylthiouracil because of its preferable side-effect profile.

» Patient advice. Warn patient to tell doctor immediately if either sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness occurs.

20.8. Medicines For Management Of Hyperparathyroidism

Cinacalcet

ATC Code : H05BX01

Tablet, 30mg, LOU 5

Indications and dosage

Adults

Secondary hyperparathyroidism (in patients with end stage renal disease on haemodialysis): Initially 30 mg once daily, dose to be adjusted every 2–4 weeks according to response; maximum 180 mg per day.

Severe hypercalcaemia in primary hyperparathyroidism: 30mg twice daily (max. per dose 90 mg 4 times a day), dose to be adjusted every 2–4 weeks according to response.

Paediatrics

Child 3-17years: *Secondary hyperparathyroidism (in patients with end stage renal disease on haemodialysis)*: 0.5mg/kg/day to be titrated every 4 weeks

Contraindications

» Hypocalcemia

» Hypersensitivity to the active ingredient or excipients in the product

Precautions

» Risk factors for QT prolongation.

» History of seizures

» History of impaired cardiac function.

» CKD patients not on dialysis.

» Hypotension.

Renal impairment: Dose adjustment not required.

Hepatic impairment: Use with caution and monitor treatment closely.

Pregnancy: Only if potential benefit outweighs the risk.

Breastfeeding: Avoid.

Adverse effects: *Common or very common: Decreased appetite, anorexia, nausea and vomiting, diarrhoea, constipation, abdominal pain, back pain, cough, dizziness, dyspnoea electrolyte imbalance, gastrointestinal discomfort, headache, hypersensitivity, hypotension, muscle spasms, myalgia, paraesthesia, rash, seizures, upper respiratory tract infection.*

Interactions with other medicines (*serious)
**Etelcacetide, *carbamazepine, *ketoconazole, *rifampicin, *clarithromycin*

Notes

» Tablet to be taken whole and not to be divided.

» To be taken with food or shortly after a meal.

Calcitriol (Vitamin D3)

See section 32, Vitamins& Minerals

20.9. Other Endocrine Medicines

Cabergoline

ATC code: G02CB03

Oral tablet**,** 0.5 mg, LOU 4

Indications and dose

Adult

*Prevention of lactation, oral***:** 1 mg, to be taken as a single dose on the first day postpartum

*Suppression of established lactation, oral***:** 250 micrograms every 12 hours for 2 days

*Hyperprolactinaemic disorders, oral***:** Initially 500 micrograms once weekly; may be taken as a single dose or as 2 divided doses on separate days, then increased in steps of 500 micrograms every month until optimal therapeutic response reached; increase dose following monthly monitoring of serum prolactin levels, usual dose 0.25–2 mg once weekly, usually 1 mg weekly; reduce initial dose and increase more gradually if patient intolerant; doses over 1 mg weekly to be given as divided dose; maximum 4.5 mg per week; higher doses are used; may administer in as many as 3 to 4 divided weekly doses

Acromegaly/Cushing disease, oral: 0.25 to 0.5 mg two times per week (max. 7 mg/week)

Paediatric

Safety and efficacy not established

Contraindications: Pre-eclampsia, history of cardiac valvular disorders, history of puerperal psychosis, history of pulmonary fibrotic disorders, history of retroperitoneal fibrotic disorders, Known hypersensitivity to cabergoline, ergot derivatives, uncontrolled hypertension, history of pulmonary, pericardial, or retroperitoneal fibrotic disorders

Precautions: Cardiovascular disease, history of peptic ulcer, history of serious mental disorders (especially psychotic disorders), Raynaud's syndrome

Hepatic impairment: Risk of increased of exposure. Consider dose reduction in severe impairment.

Pregnancy: Discontinue if pregnancy occurs during treatment (specialist advice needed).

Breast feeding: Cabergoline interferes with breastfeeding and should not be given to patients postpartum who are breastfeeding or who are planning to breastfeed.

Adverse effects: Common: nausea/Vomiting, Flatulence constipation, abdominal pain, headache, dizziness, Orthostatic hypotension, Fatigue/asthenia/arthralgia, cough/throat irritation

Serious/Rare: Congestive heart failure, Heart Valvular disorder, pleural fibrosis and effusion, peripheral edema, increased libido (including hypersexuality), weight gain, weight loss.

Interaction with other medicines: (*indicates serious)

*Ergot Derivatives may enhance the adverse/toxic effect of Bromocriptin

*Cabergoline may diminish the therapeutic effect of Metoclopramide

Sulpiride: may diminish the therapeutic effect of Cabergoline

Clarithromycin: May increase the serum concentration of Cabergoline

Desmopressin

ATC code : H01BA02

Injection, 4 mcg/mL, LOU 5

Nasal spray, 10mcg/spray, LOU 5

Indications and dose

Adult

Treatment of Central Diabetes Insipidus by subcutaneous, intramuscular or intravenous injection: 1 to 4 micrograms daily.

*By intranasal spray:*10–40 micrograms daily in 1–2 divided doses

Paediatric

Treatment of Central Diabetes Insipidus:

By intramuscular injection

Neonate: *Initially 100 nanograms once daily, adjusted according to response.*

By subcutaneous injection, or by intramuscular injection

Child 1 month–11 years: *Initially 400 nanograms once daily, adjusted according to response*

Child 12–17 years: *Initially 1–4 micrograms once daily, adjusted according to response*

By intranasal spray:

Child 1–23 months: Initially 2.5–5 micrograms 1–2 times a day, adjusted according to response

Child 2–11 years: Initially 5–20 micrograms 1–2 times a day, adjusted according to response

Child 12–17 years: Initially 10–20 micrograms 1–2 times a day, adjusted according to response

Contraindications: Hypersensitivity to desmopressin, habitual and psychogenic polydipsia, hyponatremia or those at risk, cardiac insufficiency and conditions requiring treatment with diuretics, thrombotic thrombocytopenic purpura, polyuria, Von Willebrand disease Type IIb

Precautions: Severe hypertension, coronary heart disease, electrolyte imbalance, renal impairments, pregnancy, infants and the elderly (depending on general health), oedema, abnormal conditions of nasal mucosa, patients at risk of increased intracranial pressure,

Hepatic impairment: No data available

Renal impairment: contraindicated in patients with CrCl <50ml/min

Pregnancy: Use with caution, increased risk of pre-eclampsia,

Breastfeeding: Maybe acceptable

Adverse effects: *Severe hyponatremia, headache, stomach pain, nausea, skin and general allergic reactions, conjunctivitis, asthenia, hypertension

Interactions with other medicines (*indicates serious): tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine, NSAIDs, Clofibrate, glibenclamide, lithium, antihypertensives.

Notes:

» When used without concomitant adjustment of fluid intake may lead to fluid retention and hyponatraemia, accompanied by symptoms such as weight gain, headache, nausea and oedema. In severe cases cerebral oedema, convulsions and coma may occur.

Somatropin (recombinant human growth hormone)

ATC code: H01AC01

Injection, 12mg prefilled flex-pen, LOU 5

Indications and dosage

Adult

Gonadal dysgenesis (Turner syndrome): SC, 1.4 mg/m2 daily, alternatively 45–50 mcg/kg daily

Deficiency of growth hormone: SC, initially 150–300 micrograms daily, then increased if necessary up to 1 mg daily, dose to be increased gradually, use minimum effective dose

(requirements may decrease with age)

Paediatrics

Gonadal dysgenesis (Turner syndrome):

SC injection, 1.4 mg/m2 daily, alternatively 45–50 micrograms/kg daily

Deficiency of growth hormone, SC injection or IM injection: 23–39 micrograms/kg daily, alternatively 0.7–1 mg/m2 daily

Growth disturbance in children born small for gestational age whose growth has not caught up by 4 years or later / Noonan syndrome, SC injection, Child 4–17 years: 35 micrograms/kg daily, alternatively 1 mg/m2 daily

Prader-Willi syndrome, in children with growth velocity greater than 1 cm/year, in combination with energy restricted diet, SC injection,: 1 mg/m2 daily, alternatively 35 micrograms/kg daily; maximum 2.7 mg per day

Chronic renal insufficiency (renal function decreased to less than 50%),

SC injection, child: 45–50 micrograms/kg daily, alternatively 1.4 mg/m2 daily, higher doses may be needed, adjust if necessary after 6 months.

SHOX deficiency, SC injection: child: 45–50 micrograms/kg daily

Contraindications:

- Avoid injections containing benzyl alcohol in neonates
- Evidence of tumour activity
- After renal transplantation.
- For growth promotion in children with closed epiphyses.
- Severe obesity in Prader-Willi syndrome.
- Severe respiratory impairment in Prader-Willi syndrome

Precautions:

- Acute critical illness.
- Type 1 and 2 DM and impaired glucose tolerance.
- Patients with Turner's syndrome- risk of increased intracranial hypertension.
- Fluid retention
- Hypoadrenalism
- Pancreatitis.

Renal impairment: Dosing recommendations unavailable.

Hepatic impairment: Safety and efficacy not established.

Pregnancy: Discontinue if pregnancy occurs—no information available.

Breastfeeding: No information available. Absorption from milk unlikely.

Adverse effects: *Arthralgia, carpal tunnel syndrome, fluid retention, gynaecomastia, idiopathic intracranial hypertension, musculoskeletal stiffness, myalgia, oedema, paraesthesia, hyperglycaemia, hyperinsulinism, hypothyroidism, osteonecrosis of femur, pancreatitis, slipped capital femoral epiphysis.*

Interactions with other medicines (*serious): *Insulin, corticosteroids, oral estrogen

Notes

- Somatropin is a biological medicine. Biological medicines must be prescribed and dispensed by brand name

21. Immunologicals

21.1. Diagnostic Agents

Tuberculin, Purified Protein Derivative

ATC code: V04CF01

Injection (solution),0.1-mL vial (single dose), LOU 4

Indications and dose

Adult

Test for hypersensitivity to tuberculoprotein, by intradermal injection: 5 or 10 IU (1 unit in hypersensitive patients or if TB is suspected).

Paediatric

Test for hypersensitivity to tuberculoprotein, by intradermal injection:

Child all ages: 5 or 10 units (1 unit may be used in hypersensitive patients or if TB is suspected)

Contraindications: Should not be used within 4 weeks of receiving a live viral vaccine.

Precautions: Malnutrition, the elderly, viral or bacterial infections (including HIV and severe TB), malignant disease, corticosteroid or immunosuppressant therapy: diminished sensitivity to tuberculin, avoid contact with open cuts, abraded or diseased skin, eyes or mouth. Response to tuberculin may be suppressed by live viral vaccines, viral infection, sarcoidosis.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Nausea, headache, malaise, rash, immediate local reactions (more common in atopic patients). Rarely vesicular or ulcerating local reactions, regional adenopathy, and fever.

Interaction with other medicines:

Systemic steroids: may suppress the reaction to the test.

Live vaccines: may suppress the reaction to the test and should either be administered on the same day as the test or 4 weeks after.

Notes:

- National recommendations may vary.
- Not for IV or IM injection.
- Administration of the Mantoux test consists of an intradermal injection of 5 or 10 tuberculin units into the flexor or dorsal surface of the forearm (about 4 inches below the bend of the elbow).
- Administration: According to manufacturer's directions.
- Tuberculin purified protein derivative is a sterile isotonic solution of tuberculin. It is obtained from a human strain of *M. tuberculosis* grown on a protein-free synthetic medium. Tuberculin PPD is indicated as a diagnostic aid in the detection of *M. tuberculosis* infection (Mantoux test).
- A tuberculin syringe with a ½ inch 26 or 27 gauge needle should be used to administer the test material. The bevel of the needle should be pointing upward and inserted into the most superficial layers of the skin. As the PPD is injected, a pale bleb (6–10 mm) will rise over the point of the needle, the bleb will disappear in minutes. If the bleb does not form, repeat the test at least 2 inches from the original injection site. No dressing is required.
- All tuberculins should comply with the Requirements for Tuberculins (Revised 1985) WHO Expert Committee on Biological Standardization Thirty-sixth report (WHO Technical Report Series, No. 745, 1987, Annex 1).

21.2. Sera & Immunoglobulins

Anti-Snake Venom Immunoglobulin

ATC code: J06AA03

Injection (for IV infusion), pentavalent serum (African) 10-mL vial, LOU 4

Indications and dose

Adult

Acute envenomation following snake or spider bite

Depends on the specific antivenom used; consult local protocol and manufacturers' literature

Paediatric

Acute envenomation following snake or spider bite

Children are at greater risk of severe envenoming because of smaller body mass and likelihood of physical activity immediately following a bite.

Children require the same doses of antivenom as adults and should not be given weight-adjusted doses, which may grossly underestimate antivenom requirements; the amount of antivenom required depends on the amount of venom to be neutralized, not the weight of the patient.

Contraindications: There are no absolute contraindications to antivenom treatment in significant systemic envenoming, treatment can be lifesaving. Several antivenoms are derived from rabbit, equine or ovine sources and should be used in caution in patients allergic to these animals, but do not withhold treatment in severe or potentially severe envenomation.

Precautions: Anaphylaxis, although rare, may occur, concomitant or recent use of live virus vaccines, resuscitation facilities should be immediately available. Live virus vaccines Immunoglobulins may interfere with the immune response to live virus vaccines which should be administered 3 weeks before or 3 months after immunoglobulin. Resuscitation facilities should be immediately available.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects:

Common: Rash (transient), headache, hypotension, fever, anaphylaxis or anaphylactoid reactions with hypotension, dyspnoea, urticaria, and shock (immediate or early onset), serum sickness (delayed onset, risk increases with volume of antivenom).

Abdominal pain, vomiting, arthralgia, myalgia, pain at infusion site.

Interaction with other medicines:

There are no known interactions involving a significant change in effect.

Notes:

- There are many antivenom immunoglobulins, each containing specific venom-neutralizing globulins. It is important that the specific antivenom immunoglobulin suitable for the species causing the envenomation is administered.
- All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). WHO Expert Committee on Biological Standardization Forty-third report, WHO Technical Report Series, No. 840, 1994, Annex 2.
- Acute envenomation from snakes or spiders is common in many parts of the world. The bite may cause local and systemic effects. Local effects include pain, swelling, bruising and tender enlargement of regional lymph nodes. Wounds should be cleaned and pain may be relieved by analgesics.
- If significant amounts of toxin are absorbed after a snake bite, this may result in early anaphylactoid symptoms such as transient hypotension, angioedema, abdominal colic, diarrhoea and vomiting, followed by persistent or recurrent hypotension and ECG abnormalities. Spontaneous systemic bleeding, coagulopathy, respiratory distress syndrome and acute renal failure may occur. Early anaphylactoid symptoms may be treated with epinephrine.
- Snake antivenom immunoglobulins are the only specific treatment available but they can produce severe adverse reactions. They are generally only used if there is a clear indication of systemic involvement, severe local involvement or, in regions where supplies are not limited, in patients at high risk of systemic or severe local involvement. There are many antivenom immunoglobulins each containing specific venom-neutralizing globulins. It is important that the specific antivenom immunoglobulin suitable for the species causing the envenomation is administered. In countries where there are a number of venomous snake species (e.g., Australia), a polyvalent immunoglobulin is also available to be used. This is used when the snake species is not known, the specific antivenom is not available or is not available in sufficient quantity to treat the envenomation. Risk of anaphylactoid reaction can be reduced by adequate dilution of antivenom before infusion.
- Spider bites may cause either necrotic or neurotoxic syndromes depending on the species involved. Supportive and symptomatic treatment is required and in the case of necrotic syndrome, surgical repair may be necessary. Spider antivenom immunoglobulin, suitable for the species involved, may prevent symptoms if administered as soon as possible after envenomation.

21.3. Vaccines

21.3.1. Recommended For All

BCG Vaccine , (Bacillus Calmette-Guérin)

ATC code: J07AN01, L03AX03

Powder for injection (live attenuated) (+diluent), 1-mL vial (multidose), LOU 2

Indications and dose

Adult

Active immunization against TB: Reconstitute and administer according to manufacturer's directions.

Paediatric

Immunization against TB: Percutaneous

Neonate or **infant:** 0.05 mL

Child: 0.1 mL

Contraindications: HIV infection, immunodeficiency, patients receiving immunosuppressive therapy, generalized septic skin conditions, current isoniazid treatment, history of anaphylaxis to any component of the vaccine, pregnancy, bone marrow or lymphoid malignancy.

Precautions: Pregnancy, Eczema or skin infection (vaccine site must be lesion-free), concomitant administration of other vaccines (either administer concurrently with other vaccines or separate by 4 weeks).

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Rarely lymphadenitis, local ulceration, disseminated BCG infection in immunodeficient individuals, and osteitis.

Common: Ulcer at injection site (2–6 weeks after vaccination), enlargement of regional lymph nodes, transient injection site reactions (pain, redness, itching, swelling or burning). Transient fever, fainting.

Rare: Abscess, keloid formation, disseminated infection, lymphadenitis, local ulceration, disseminated BCG infection in immunodeficient individuals, osteitis, anaphylactoid reactions.

Interaction with other medicines (*indicates serious): Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* Azathioprine: avoid use of live vaccines with

azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* Ciclosporin: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* Dexamethasone: high doses of dexamethasone impair immune response, avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* Hydrocortisone: high doses of hydrocortisone impair immune response, avoid use of live vaccines.

* Isoniazid: concurrent treatment with isoniazid can inactivate the vaccine.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* Prednisolone: high doses of prednisolone impair immune response, avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes:

- All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances, these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers. www.who.int/biologicals/publications/trs/areas/en/index.html
- TB is a bacterial infection caused by *M. tuberculosis,* transmitted from person to person through respiratory contact. Where TB remains highly prevalent, routine immunization of infants within the first year of life with BCG vaccine, derived from bacillus Calmette-Guérin (an attenuated strain of *Mycobacterium bovis*) reduces the incidence of meningeal and miliary TB in early childhood. The efficacy against pulmonary TB is doubtful, the mainstay of the TB control programme is case-finding and treatment.
- WHO recommends that all infants in highly endemic countries should receive a single dose of BCG vaccine as soon as possible after birth. In low-endemic countries, BCG vaccine can be given to infants and children at high risk of TB exposure. Infants known to be HIV-infected (with or without symptoms) should not receive BCG vaccination. Infants born to known HIV-infected mothers should only be immunized if no signs or symptoms suggestive of HIV infection are present and after taking into consideration the likelihood of the infant being infected with HIV, and the potential risk of exposure to TB. If HIV infection status can be established with early virological testing, BCG vaccine can be administered once HIV infection has been ruled out.
- Infants exposed to smear-positive pulmonary TB shortly after birth should not receive BCG vaccination until completion of 6 months of prophylactic isoniazid treatment.
- BCG vaccine may be given simultaneously with other live vaccines, but if not given at the same time they should be given 4 weeks apart. When BCG vaccine is given to infants, there is no need to delay routine primary immunizations.

DPT+ HiB + Hep B Vaccine (Pentavalent)

ATC code: J07CA11

Injection (suspension), 5-mL vial (10 doses), LOU 2

Each dose of 0.5 mL contains: Diphtheria Toxoid, Tetanus Toxoid, B. pertussis (whole cell), HBsAg (rDNA), Purified capsular Hib Polysaccharide

Indications and dose

Paediatric

Immunization against Diptheria, Pertussis, Tetanus, Hemophilus Influenzae type B and Hepatitis B, IM

Infants: 0.5 mL at 6, 10, and 14 weeks of birth

Contraindication: Vaccines are contraindicated in individuals with known severe hypersensitivity to any component, consult the manufacturer's literature for the specific composition of individual vaccines.

Precautions: If a serious adverse event occurs (such as severe allergy or anaphylaxis) following a dose of the vaccine, subsequent doses should not be given. In addition, certain components of the vaccine (for example, aluminium adjuvant, antibiotics, excipients, or preservatives) occasionally cause reactions. Some vaccines are prepared using hens' eggs, caution is required when the patient is known to have egg sensitivity.

Adverse effects: Adverse reactions are usually mild and commonly include injection site reactions (such as pain, erythema, and inflammation), fever, and malaise. These reactions generally occur within 1–2 days of immunization. Serious reactions are rare, but hypersensitivity reactions including anaphylaxis have been reported.

Interaction with other medicines:
Immunosuppressants, varicella vaccine

Notes:

- Pentavalent Vaccine should be started for any child aged more than 6 weeks and can be given up to 1 year of age
- Patient information: A child whose vaccination schedule has been initiated with DPT/hepatitis B vaccine will continue to receive subsequent doses of DPT/hepatitis B and not pentavalent vaccine

Hepatitis B Vaccine

(Also referred to as adsorbed recombinant DNA hepatitis B surface antigen)

ATC code: J07BC01

Injection (suspension), single-dose vial and multidose vial, LOU 2

Indications and dose

Adult

Active immunization against hepatitis B, post-exposure prophylaxis (The actual dose used depends on the formulation available.): 3 doses of 1 mL, with an interval of 1 month between the first and second dose and 5–11 months between the second and third doses

Paediatric

Primary immunization against Hepatitis B, IM

Neonate, infant, or **child from birth:** One monovalent dose at birth, then two or three subsequent doses of monovalent or combined hepatitis B vaccine administered according to schedules of national routine immunization programmes; generally, subsequent doses after birth dose are given at 2, 4, and 6 or 12 months of age, depending on the vaccine used

Note: Combination hepatitis B vaccines should not be used for the birth dose. This dose should be provided using the monovalent hepatitis B vaccine.

Alternatively, if birth dose is missed (three-dose schedule), IM

Neonate, infant, or **child over 8 days:** Three doses with 1 month duration between the first and second dose, and the third dose to be given 5 months after the second dose (or at a minimum at least 2 months after the second dose)

Hepatitis B prophylaxis for infants born to hepatitis B surface antigen-positive mother, IM

Neonate: One dose of vaccine with hepatitis B immunoglobulin (in the opposite thigh) within 12 hours of birth (yet preferably immediately after birth), then three subsequent doses as per primary immunization (as above)

Post-exposure prophylaxis (other than at birth), IM

Child all ages: Administer vaccine at age appropriate dose, with the second dose given at 1 month and the third dose given at 2 months after the initial dose; for those at continued risk, a fourth dose should be given 12 months after the first dose

Note: Hepatitis B immunoglobulin should also be administered with the first dose.

Percutaneous/ocular/mucous membrane exposure, IM

Child all ages: Administer first dose of vaccine within 7 days and hepatitis B immunoglobulin within 72 hours

Sexual exposure, IM

Child all ages: Administer first dose of vaccine and hepatitis B immunoglobulin within 14 days

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Acute febrile illness (postpone all vaccinations until patient is well). A reduced immunogenicity of the vaccine may occur in individuals with immunodeficiency including advanced HIV infection, diabetes, chronic liver disease or chronic renal failure.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Common: Transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare: Malaise, myalgia, arthralgia, lymphadenopathy, peripheral neuropathy, delayed hypersensitivity reactions, allergic reactions including anaphylaxis.

Interaction with other medicines: There are no known interactions where it is recommended to avoid concomitant use.

Notes:

- All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances, these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.
- www.who.int/biologicals/publications/trs/areas/en/index.html
- Different products may contain different concentrations of antigen. Consult manufacturer's literature for further information.
- Administration: The vaccine should be given in the deltoid region in adults and older children, anterolateral thigh is the preferred site in infants and young children, it should not be injected into the buttock (vaccine efficacy is reduced).
- WHO recommends hepatitis B vaccine is given as part of the national infant immunization programme. Catch-up immunization should be

considered for older age groups, or high-risk individuals who have not been previously immunized in countries with intermediate or low hepatitis B endemicity. High-risk groups may include but are not limited to: household or sexual contacts of known carriers, haemodialysis patients, HIV-positive, immunosuppressed, injecting drug users, chronic liver disease, regular blood product recipients.

» Two types of hepatitis B vaccines are available: plasma-derived and recombinant vaccines. Both types are highly effective but the recombinant vaccine is most commonly used. Hepatitis B vaccine is available as a monovalent or a fixed-combination vaccine with other antigens such as *Haemophilus influenzae* type b, poliomyelitis, diphtheria, pertussis and tetanus. The monovalent vaccine should be used when immunizing infants at birth. Recommended schedules vary considerably between countries, but the minimum recommended interval between doses is 4 weeks. In countries where a high proportion of hepatitis B infections are acquired perinatally, a three-dose or four-dose schedule is recommended with the first dose given within 24 hours of birth. The other doses are usually given at the same time as diphtheria-tetanus-pertussis (DTP) or other vaccines.

Human Papilloma Virus (HPV) Vaccine (Quadrivalent)

ATC code: J07BM03

Injection, singe or multidose vial, LOU 2 (containing HPV types 6, 11, 16, and 18)

Indications and use

Paediatric

Prevention of cervical cancer, genital warts, and other pre-cancerous lesions caused by human papilloma virus (HPV) types 6, 11, 16, and 18.

HPV vaccine will be most effective if given before sexual activity starts.

The first dose is given to females aged 10 to 14 years, the second and third doses are given 6 months after the first dose, all 3 doses should be given within a 12-month period.

Contraindications: Pregnancy: not known to be harmful, but vaccination should be postponed until completion of pregnancy

Precautions: HPV vaccine is available as a bivalent vaccine or a quadrivalent vaccine. The two vaccines are not interchangeable and one vaccine product should be used for an entire course.

Adverse effects: Not known to be harmful, but vaccination should be postponed until completion of pregnancy

Notes:

» Bivalent vaccine is licensed for use in females for the prevention of cervical cancer and other precancerous lesions caused by HPV types 16 and 18. Quadrivalent vaccine is licensed for use in females for the prevention of cervical cancer, genital warts, and precancerous lesions caused by HPV types 6, 11, 16, and 18.

» If the course is interrupted, it should be resumed but not repeated, allowing the appropriate interval between the remaining doses. Where there are significant challenges in scheduling vaccinations, or a high likelihood that the third dose will not be given, the third dose of bivalent vaccine can be given 3 months after the second dose.

» The duration of protection has not been established, but current studies suggest that protection is maintained for at least 6 years after completion of the primary course. As the vaccines do not protect against all strains of HPV, routine cervical screening should continue.

Measles + Rubella Vaccine (MR)

ATC code: J07BD53

Powder for injection + diluent, 5-mL vial (10 doses), LOU 2

Paediatric

Immunisation against measles and rubella

0.5 mL administered subcutaneously into the right upper arm (deltoid muscle)

1st dose: At 9 months or at first contact after 9 months for children under 5 years.

2nd dose: At 18 months or first contact after 18 months.

Contraindication: Antibody response to measles component may be reduced after immunoglobulin administration or blood transfusion– leave an interval of at least 3 months before MMR immunization.

Precautions: MMR vaccine should not be administered on the same day as yellow fever vaccine, there should be a 4-week minimum interval between the vaccines.

Hepatic impairment: Dose adjustment not necessary.

Renal impairment: Dose adjustment not necessary.

Adverse effects: Parotid swelling (usually in the third week), sleep disturbances, unusual crying in infants. Rare Arthropathy (2 to 3 weeks after immunisation), idiopathic thrombocytopenic purpura, optic neuritis, peripheral neuritis.

Interaction with other medicines:

Abatacept, cyclosporine, tacrolimus, cancer chemotherapy, corticosteroids, immune globulin.

Pneumococcal Vaccine (10 Valent Adsorbed Conjugate)

ATC code: J07AL02

Injection (suspension), 2-mL vial (4 doses), LOU 2

Indications and use

Paediatric

Active and primary immunization against Streptococcus pneumoniae, IM

Infant: 3 doses of 0.5 mL given IM into the upper outer aspect of the right thigh, each a minimum of 4 weeks apart

First dose: At 6 weeks of life or at first contact with unvaccinated child under 5 years

Second dose: At 10 weeks or 4 weeks after PCV1

Third dose: At 14 weeks or 4 weeks after PCV2

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Acute febrile illness: postpone all vaccinations until patient is well.

23-valent (unconjugated) polysaccharide vaccine is not recommended for children under 2 years.

Hepatic impairment: Dose reduction not required.

Renal impairment: Dose reduction not required.

Adverse effects: Myalgia, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare: Cellulitis, seizures, angioedema, allergic reactions including anaphylaxis.

Interaction with other medicines:

There are no known interactions where it is recommended to avoid concomitant use.

Notes:

- All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances, these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.
- There are three variants of the conjugated vaccine:
  - 7-valent conjugate vaccine known as PCV-7 or 7vPCV,
  - 10-valent conjugate vaccine known as PCV-10 or 10vPCV,
  - 13-valent conjugate vaccine known as PCV-13 or 13vPCV.
- There is also a 23-valent unconjugated pneumococcal polysaccharide vaccine known as 23vPPV.
- Streptococcus pneumoniae causes serious infection such as pneumonia and meningitis, especially in young children under 2 years of age, the elderly and individuals with immunodeficiency. The bacteria are transmitted via respiratory secretions. WHO recommends that pneumococcal conjugate vaccine should be included in national routine childhood immunization programmes. The 7-valent conjugate vaccine (PCV-7) provides effective protection in young children, the primary schedule usually consists of three doses, each administered at intervals of at least 4 weeks, other three-dose schedules have been shown to be effective and are in use in some countries. A booster dose given after 12 months of age may improve the immune response. Immunization should be initiated before 6 months of age and may start as early as 6 weeks of age. The vaccine can be given to HIV-infected individuals.
- A single dose of PCV-7 can be given to children aged 12–24 months of age who have not been previously vaccinated and children 2–5 years of age at high risk of pneumococcal disease.
- A 23-valent (unconjugated) polysaccharide vaccine is also available for adults and children over 2 years of age at risk of pneumococcal infection (it provides a suboptimal response in infants).

Pneumococcal Vaccine (13 Valent or Higher Absorbed Conjugate)

ATC code: J07AL02

Injection, single or multidose vial, LOU 2

Indications and use

Adult

Active immunization against Streptococcus pneumoniae, IM: 0.5 mL as a single dose

Immunization is recommended for adults 19 to <65 years of age with specified underlying medical conditions.

Paediatric

Primary immunization against Streptococcus pneumoniae, IM injection using pneumococcal polysaccharide conjugated vaccine (13vPCV):

Infant: Three doses of 0.5 mL, each a minimum of 4 weeks apart, e.g., at 6, 10 and 14 weeks of age or 2, 4 and 6 months of age; booster can be given at 12 months of age

Infant presenting late for vaccination: Two doses of 0.5 mL at least 4 weeks apart followed by a third dose at 13 months

Child 1–5 years, previously not vaccinated or not completed primary course: 0.5 mL as a single dose or 0.5 mL separated by 2 months in the immunocompromised or those with asplenia or splenic dysfunction

Revaccination of children who are at increased risk of pneumococcal disease and its complications due to underlying health conditions, SC or IM injection using 23-valent pneumococcal polysaccharide vaccine (23vPPV)

Child over 2 years: 0.5 mL as a single dose and subsequently every 5 years

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Acute febrile illness: postpone all vaccinations until patient is well.

23-valent (unconjugated) polysaccharide vaccine is not recommended for children under 2 years.

Hepatic impairment: Dose reduction not required.

Renal impairment: Dose reduction not required.

Adverse effects: Myalgia, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare: Cellulitis, seizures, angioedema, allergic reactions including anaphylaxis.

Interaction with other medicines: There are no known interactions where it is recommended to avoid concomitant use.

Notes:

- All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances, these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.
- There are three variants of the conjugated vaccine:
  - 7-valent conjugate vaccine known as PCV-7 or 7vPCV,
  - 10-valent conjugate vaccine known as PCV-10 or 10vPCV,
  - 13-valent conjugate vaccine known as PCV-13 or 13vPCV.
- There is also a 23-valent unconjugated pneumococcal polysaccharide vaccine known as 23vPPV.
- Streptococcus pneumoniae causes serious infection such as pneumonia and meningitis, especially in young children under 2 years of age, the elderly and individuals with immunodeficiency. The bacteria are transmitted via respiratory secretions. WHO recommends that pneumococcal conjugate vaccine should be included in national routine childhood immunization programmes. The 7-valent conjugate vaccine (PCV-7) provides effective protection in young children, the primary schedule usually consists of three doses, each administered at intervals of at least 4 weeks, other three-dose schedules have been shown to be effective and are in use in some countries. A booster dose given after 12 months of age may improve the immune response. Immunization should be initiated before 6 months of age and may start as early as 6 weeks of age. The vaccine can be given to HIV-infected individuals.
- A single dose of PCV-7 can be given to children aged 12–24 months of age who have not been previously vaccinated and children 2–5 years of age at high risk of pneumococcal disease.
- A 23-valent (unconjugated) polysaccharide vaccine is also available for adults and children over 2 years of age at risk of pneumococcal infection (it provides a suboptimal response in infants).

Polio Vaccine (IPV) (Inactivated)

ATC code: J07BF03

Injection, multidose vial, LOU 2

Injection, inactivated poliomyelitis virus, types 1, 2, and 3.

Indications and use

Adult

Routine immunization in adults is not recommended

Active immunization against poliomyelitis in unimmunized or incompletely immunized adults exposed to wild poliovirus, IM/SC

0.5ml two doses 1 – 2 months apart with third dose 6 – 12 months later

Paediatric

Primary immunization of children against poliomyelitis

0.5 mL by IM injection into the upper outer aspect of the right thigh, at 14 weeks or at first contact with an unvaccinated child below 1 year

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Acute febrile illness (postpone all vaccinations until patient is well). A reduced immunogenicity of the vaccine may occur in individuals with immunodeficiency including advanced HIV infection, diabetes, chronic liver disease or chronic renal failure.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Common: Transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare: Malaise, myalgia, arthralgia, lymphadenopathy, peripheral neuropathy, delayed hypersensitivity reactions, allergic reactions including anaphylaxis.

Interaction with other medicines: Immunosuppressant medicines e.g. corticosteroids and anticancer medicines

Polio, Oral (OPV) (Live Attenuated)

ATC code: J07BF02

Oral drops, 10-mL vial, (20 doses), LOU 2

Indications and dose

Adult

Primary immunization of unimmunized adult against poliomyelitis, oral: Doses, each of 3 drops, with an interval of at least 4 weeks between each dose

Paediatric

Primary immunization of children against poliomyelitis, oral

Infant or **child:** 2 drops at birth or within 2 weeks of birth and at 6 weeks or at first contact with unvaccinated child under 5 years

2nd dose: At 10 weeks or 4 weeks after OPV1 and

3rd dose: At 14 weeks or 4 weeks after OPV2

Reinforcing immunization of children against poliomyelitis, oral

Child: 3 drops at least 3 years after completion of primary course and a further 3 drops at 15–19 years of age

Contraindications: Primary immunodeficiency or immunosuppression

Precautions: Not to be taken with food which contains a preservative, hypersensitivity to any antibiotic present in vaccine, pregnancy

Adverse effects: Rarely, vaccine-associated poliomyelitis in recipients of vaccine and contacts of recipients.

Interaction with other medicines: Immunosuppressant medicines e.g. corticosteroids and anticancer medicines

Rotavirus Vaccine

ATC code: J07BH01

Oral suspension, 5-dose vial, LOU 2

Indications and dose

Paediatric

Immunization against gastroenteritis-caused by rotavirus, 1 mL given as three doses

1st dose: At 6 weeks of life or at first contact with unvaccinated child under 1 year

2nd dose: At 10 weeks or 4 weeks after Rota 1

Contraindications: History/predisposition to intussusception, severe combined immunosuppression.

Precautions: Postpone vaccination in diarrhea, vomiting, immunosuppression with the exception of severe combined immunodeficiency: in immunosuppressed patients.

Hepatic impairment: Dose adjustment not necessary

Renal impairment: Dose adjustment not necessary

Adverse effects: Abdominal cramps, abdominal pain, diarrhea, nausea, vomiting.

Interaction with other medicines: Abatacept, Adalimumab, Aldesleukin, Alefacept, Alemtuzumab, Anakinra, cortisone, cyclophosphamide, cyclosporine, Dacarbazine, Dactinomycin, Dasatinib, Daunorubicin, deflazacort, docetaxel, doxo\rubicin, epirubicin, etanercept, Etoposide, everolimus, flucytosine, fludarabine, fludrocortisone, flurouracil, fluticasone, gemcitabine, linezolid, leflunomide, methylprednisolone, mycophenolic acid,

Tetanus + Diphtheria (Td) Vaccine

ATC code: J07AM51

Injection, 10-mL vial (20 doses), LOU 2

Indications and dose

Adult

Tetanus prophylaxis in wound management. Active immunity against diphtheria and tetanus when pertussis vaccine is contraindicated.

Primary immunization for Patients previously not immunized should receive 2 primary doses of 0.5 mL each, given at an interval of 4–6 weeks, third (reinforcing) doses of 0.5 mL 6–12 months later.

Paediatric

Infants and Child ≤ 6 years: Primary immunization: 6 weeks to 1 year: three 0.5 mL doses at least 4 weeks apart, administer reinforcing doses 6–12 months after the third injection.

Child 1–6 years: two 0.5 mL doses at least 4 weeks apart, reinforcing dose 6–12 months after second injection, Booster immunization: 4–6 years: 0.5 mL, not necessary if the fourth dose was given after fourth birthday,

routinely administer booster doses at 10-year intervals

Child > 7 years:

Booster immunization: 0.5 mL every 10 years, to be given to children 11–12 years of age if at least 5 years have elapsed since last dose of toxoid containing vaccine.

Contraindications: hypersensitivity to diphtheria, tetanus toxoid.

Precautions: bleeding disorders or anticoagulant therapy.

Adverse effects: dizziness, seizure, rash, nausea, vomiting, local reactions, myalgia, arthralgia.

Interaction with other medicines: antimetabolites, alkylating agents, cytotoxic drugs, corticosteroids, irradiation.

Tetanus + Diphtheria + Pertussis (Tdap) Vaccine

ATC code: J07AM51

Injection, 0.5 mL (single dose), LOU 2

Indications and dose

Paediatric

Active immunization against diphtheria, tetanus, and pertussis, IM

Child 6 weeks to <7 years: 0.5 mL

Primary series: 3 doses, usually given at 2, 4, and 6 months of age; may be given as early as 6 weeks of age and repeated every 4–8 weeks; use same product for all 3 doses

Booster series

Fourth dose: Given at ≈15–20 months of age, but at least 6 months after third dose

Fifth dose: Given at 5–6 years of age, prior to starting school or kindergarten; if the fourth dose is given at ≥4 years of age, the fifth dose may be omitted

Contraindications: children > 7 years of age.

Precautions: children with coagulation disorders, seizure disorder.

Renal impairment: Dose adjustment not necessary

Hepatic impairment: Dose adjustment not necessary.

Adverse effects: drowsiness, irritability, decreased appetite, redness, swelling, fever, vomiting, pain, redness, and tenderness.

Interaction with other medicines: anticoagulants, corticosteroids and immunosuppressant

21.3.2. Recommended For Some Regions

Yellow Fever Vaccine (Live, Attenuated)

ATC code: J07BL01

Injection, single or multidose vial, LOU 2

Indications and dose

Adult

Active immunization against yellow fever, SC into the left upper arm: 0.5 mL for 1 dose

Paediatric

Active immunization against yellow fever, Sc into the left upper arm

Infant at 9 months of first contact after 9 months: in Baringo, Elgeyo Marakwet, West Pokot and Turkana (high-risk counties)

Child 6–8 months (administered on expert advice): Infants under 9 months should be vaccinated only if the risk of yellow fever is high and unavoidable (consult product literature or local protocols)

Child 9 months–17 years: 0.5 mL for 1 dose

Contraindications: Hypersensitivity to the vaccine, egg or chick embryo protein, or any component, immunosuppressed patients, children less than 6 months of age.

Precautions: Patients with thymic disorders including myasthenia gravis, thymoma or prior thymectomy, concomitant administration of other live vaccines

Hepatic impairment: Dose reduction not required.

Renal impairment: Dose reduction not required.

Adverse effects: Common: Headache, myalgia, weakness, nausea, diarrhoea.

Abdominal pain, vomiting, malaise, influenza-like symptoms, arthralgia.

Rare: Allergic reactions (rash, urticaria, asthma, anaphylactoid reaction), yellow fever vaccine-associated neurotropic disease or viscerotropic disease (see below).

Yellow fever vaccine-associated neurotropic disease Occurs within 30 days of vaccination and may be fatal, symptoms include high fever, headache, confusion, encephalopathy, meningitis and seizures.

Yellow fever vaccine-associated viscerotropic disease Occurs within 10 days of vaccination and may be fatal, symptoms include fever, myalgia, headache, liver and muscle cytolysis, thrombocytopenia, acute renal failure and respiratory failure.

Interaction with other medicines (*indicates serious):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* Azathioprine: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response

* Ciclosporin: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* Dexamethasone: high doses of dexamethasone impair immune response, avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* Hydrocortisone: high doses of hydrocortisone impair immune response, avoid use of live vaccines.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* Prednisolone: high doses of prednisolone impair immune response, avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes:

- Note Dose should be given at least 10 days before travel to yellow fever endemic area.
- In conformity with section 32 of the Public Health Act Cap 242 of the Laws of Kenya, all travelers departing the country must have a valid certificate against yellow fever.
- All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances, these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.
- www.who.int/biologicals/publications/trs/areas/en/index.html
- Also referred to as yellow fever 17D.
- Yellow fever 17D vaccine is a live attenuated vaccine, which offers protection from 10 days after vaccination, for at least 10 years.
- WHO recommends that all countries with endemic yellow fever should incorporate yellow

fever vaccine into their national immunization programme, the vaccine should be given to infants 9–12 months of age and can be given at the same time as the measles vaccine. Yellow fever vaccine is also recommended for people at high risk of yellow fever exposure, people living in or travelling to endemic areas. During epidemics, mass vaccination campaigns should be initiated as early as possible.

» Immunization is not recommended for infants 6–8 months of age or during pregnancy, except during an epidemic when the risk of transmission may be very high. Yellow fever vaccine is contraindicated in individuals with severe immunodeficiency or severe egg allergy (HIV-infected individuals may be vaccinated if CD4 cell counts are over 200 cells/mm3).

21.3.3. Recommended For Some High-Risk Populations

Cholera Vaccine

ATC code: J07AE01

Oral suspension, 1.5-mL vial (single-dose vial), LOU 2

inactivated (WC/rBS) cholera virus.

Note: Formulations vary between products and manufacturers and dilution may be required before administration, consult manufacturer's literature

Indications and dose

Active immunization against cholera.

Dukoral (WC/rBS)

Primary immunization against *V. cholerae.*

Adult

Immunization against cholera, oral

Immunisation against cholera (for travelers to endemic or epidemic areas on the basis of current recommendations)

1 dose every 1–6 weeks for 2 doses, if more than 6 weeks have elapsed between doses, the primary course should be restarted, immunisation should be completed at least one week before potential exposure

Booster

A single booster dose can be given within 2 years after primary course, if more than 2 years have elapsed since the last vaccination, the primary course should be repeated.

Paediatric

Active immunization against cholera, oral:

Child 2–5 years: three doses given > 7 days apart (but < 6 weeks apart)

Child 6–12 years: two doses given > 7 days apart (but < 6 weeks apart).

Note if the interval between the primary immunization doses is delayed for > 6 weeks, primary immunization should be restarted.

Continued risk of V. cholerae infection, oral:

Child 2–5 years: one booster dose every 6 months. If the interval between the primary immunization series and the booster immunization is > 6 months, primary immunization must be repeated

Child 6–12 years: one booster dose after 2 years. If the interval between the primary immunization series and booster immunization is > 2 years, primary immunization must be repeated.

Shanchol

Paediatric

Immunization against *V. cholerae, Oral:*

Child all ages: two doses given 14 days apart. A booster dose is recommended after 2 years.

Contraindications: Anaphylaxis to the vaccine or any component of the vaccine.

Hepatic impairment: Dose reduction not necessary

Renal impairment: Dose reduction not necessary.

Adverse effects: Common Abdominal discomfort, diarrhea, headache. Also mild transient GI disturbances reported.

Rare Allergic reactions including anaphylaxis.

Interaction with other medicines (*indicates serious):

* Ciclosporin: avoid use of live vaccines with ciclosporin (impairment of immune response).

* Dexamethasone: high doses of dexamethasone impair immune response, avoid use of live vaccines.

* Hydrocortisone: high doses of hydrocortisone impair immune response, avoid use of live vaccines.

Oral typhoid vaccine: inactivated vaccine buffer may affect transit time, allow at least 8 hours between the administration of cholera and typhoid vaccines.

Notes:

» All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances, these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.www.who.int/biologicals/publications/trs/areas/en/index.html

» Dukoral: intake of food and drink should be avoided for 1 hour before and after vaccination. The sodium hydrogen carbonate buffer is supplied as effervescent granules, which should be dissolved in a glass of water (approximately 150 mL).

» Dukoral should be mixed with the sodium hydrogen carbonate solution and drunk. Protection may be expected about 1 week after the last scheduled dose. Dukoral has been shown to cross-protect against enterotoxigenic *Escherichia coli*.

» Cholera is caused by *Vibrio cholerae* and is closely associated with poor sanitation. It is transmitted by faecal contamination of water and food, person-to-person transmission is.

- Cholera control should be a priority in areas where the disease is endemic. Given the availability of two oral cholera vaccines and data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, immunization with these vaccines should be used in conjunction with other prevention and control strategies in areas where the disease is endemic and should be considered in areas at risk for outbreaks.
- Vaccination should not disrupt the provision of other high-priority health interventions to control or prevent cholera outbreaks. Vaccines provide a short-term effect that can be implemented to bring about an immediate response while the longer-term interventions of improving water and sanitation, which involve large investments, are put into place.
- Although all age groups are vulnerable to cholera, where resources are limited immunization should be targeted at high-risk children aged ≥ 1 year (Shanchol or mORCVAX) or ≥ 2 years (Dukoral). (For vaccine schedules and administration, see recommendations made by the manufacturers.)
- Immunization for travelers is only recommended for individuals at increased risk of exposure, particularly emergency relief and health-care workers in refugee situations or individuals at particular risk of complications of diarrhoeal disease including those with inflammatory bowel disease, poorly controlled diabetes, cardiovascular disease or immune suppression.
- Injectable cholera vaccine is not recommended by WHO because it provides unreliable protection and does not prevent transmission of infection.

Hepatitis A Vaccine

ATC code: J07BC02

Injection, 80 units (paediatrics), 160 units (adults), LOU 2

The dose of vaccine, vaccination schedule, ages for which a vaccine is licensed, and whether there is a paediatric and/or adult formulation varies from manufacturer to manufacturer.

Various formulations of hepatitis A vaccines are available, which may contain different adsorbents or concentrations of antigen. Consult manufacturer's literature for further information about specific dosages, booster intervals, administration, and use in children.

Indications and dose

Adult

Active immunization against hepatitis A, IM injection:

AVAXIM ®

By IM injection: Initially 0.5 mL for 1 dose, then 0.5 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose.

The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders; not to be injected into the buttocks since vaccine efficacy is reduced.

HAVRIX MONODOSE ®

By IM injection: Initially 1 mL for 1 dose, then 1 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose, the deltoid region is the preferred site of injection; not to be injected into the gluteal region. The subcutaneous route may be used for patients with bleeding disorders.

VAQTA® ADULT

By IM injection: Initially 1 mL for 1 dose, then 1 mL after 6–18 months, dose given as booster, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders (but immune response may be delayed)

Paediatric

Active immunization against hepatitis A, IM Injection:

AVAXIM ®

By IM Injection:

Child 16–17 years: Initially 0.5 mL for 1 dose, then 0.5 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose.

HAVRIX JUNIOR MONODOSE ®

By IM injection:

Child 1–15 years: Initially 0.5 mL for 1 dose, then 0.5 mL after 6–12 months, dose given as booster which may be delayed by up to 3 years if not given after recommended interval following primary dose. The deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the gluteal region. The subcutaneous route may be used for patients with bleeding disorders

HAVRIX MONODOSE ®

By IM injection:

Child 16–17 years: Initially 1 mL for 1 dose, then 1 mL after 6–12 months, dose given as booster which may be delayed by up to 3 years if not given after recommended interval following primary dose, the deltoid region is the preferred site of injection; not to be injected into the gluteal region. For patients with bleeding disorders, the subcutaneous route may be used

VAQTA ® PAEDIATRIC

By IM injection:

Child 1–17 years: Initially 0.5 mL for 1 dose, then 0.5 mL after 6–18 months, dose given as booster, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders (but immune response may be reduced)

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Serious active infection, cardiovascular disease, pulmonary disorders, previous unexplained hepatitis or jaundice, previous hepatitis A infection, previous confirmed hepatitis A injection (likely to confer immunity: vaccine not needed).

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Common: Headache, malaise, fatigue, nausea, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Urticaria, rash, myalgia.

Rare: Encephalopathy, allergic reactions including anaphylaxis.

Interaction with other medicines:

There are no known interactions where it is recommended to avoid concomitant use.

Notes:

- All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances, these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.
- www.who.int/biologicals/publications/trs/areas/en/index.html
- There are a number of combination products that are available (often denoted by abbreviations) and these vary depending on country.
- Hepatitis A is caused by hepatitis A virus. It is transmitted via the faecal-oral route from person to person through close physical contact and ingestion of contaminated food and water. Those at increased risk of infection include parenteral drug abusers, individuals who change sexual partners frequently, individuals exposed to untreated sewage, those living in closed communities, travelers to endemic countries, laboratory staff working with the virus, patients with haemophilia treated with plasma-derived clotting factors, and individuals who work with primates. Patients with chronic liver disease including chronic hepatitis B or chronic hepatitis C are at risk of severe liver disease if infected with hepatitis A.
- In highly endemic countries, exposure is almost universal before 10 years of age and large-scale immunization programmes should not be undertaken. In areas of intermediate endemicity with periodic outbreaks, control of hepatitis A may be achieved through widespread vaccination programmes, but is most successful in small, self-contained communities. In countries with low endemicity, vaccination for high-risk populations may be recommended.
- Several vaccines are available, which provide long-lasting protection, but none are licensed for use in children under 1 year of age, the dose of the vaccine and vaccination schedule varies between manufacturers. A single dose of vaccine provides a protective antibody response within a month, the manufacturers recommend a second dose 6–18 months later to ensure long-term protection.

Malaria Vaccine

ATC code: Not assigned

Injection, 1-mL vial (2 doses), LOU 2

Limited information on the Malaria vaccine.

Indications and dose

Paediatric

Immunization against malaria

Infant: Three doses given at 6, 7, and 9 months of age and fourth dose given at 24 months

Meningococcal Meningitis Vaccine

ATC code: J07AH

Injection, single or multidose, LOU 2

Indications and dose

Doses depend on the brand of vaccine selected

Adult

Meningococcal group B vaccine (rDNA, component, adsorbed)

BEXSERO ®

Immunization against Neisseria meningitidis, primary immunization (in unimmunized patients), By Deep IM injection: 0.5 mL for 2 doses, separated by an interval of at least 1 month. Injected preferably into deltoid region

TRUMENBA ®

Immunization against Neisseria meningitidis, primary immunization, By Deep IM injection: 0.5 mL for 2 doses, separated by an interval of 6 months, alternatively 0.5 mL for 2 doses, separated by an interval of at least 1 month, followed by 0.5 mL as a third dose, given at least 4 months after the second dose, injected preferably into deltoid region, a booster dose should be considered for individuals at continued risk—consult product literature

Meningococcal Group C Vaccine

Patients with confirmed serogroup C disease (who have previously been immunized), By IM injection: **18–24 years:** 0.5 mL for 1 dose, dose to be given before discharge from hospital

Meningococcal Groups A With C And W135 And Y Vaccine

MENVEO ®

Immunization against Neisseria meningitidis in an unimmunized patient, By IM injection: **18–24 years:** 0.5 mL for 1 dose, booster dose is not required

Immunization against Neisseria meningitidis in those at risk of exposure to prevent invasive disease, By IM injection: 0.5 mL for 1 dose.

Dose preferably injected into deltoid region

Patients attending university for the first time (who have not received the routine meningococcal groups A with C and W135 and Y conjugate vaccine over the age of 10 years), By IM injection: **18–24 years:** 0.5 mL for 1 dose

NIMENRIX®

*Immunization against Neisseria meningitidis in an unimmunized patient, By IM injection:***18–24 years:** 0.5 mL for 1 dose, booster dose is not required

immunization against *Neisseria meningitidis* in those at risk of exposure, *By IM injection:* 0.5 mL for 1 dose, to be injected preferably into deltoid region, then 0.5 mL after 1 year if required for 1 dose, second dose should be considered in those who continue to be at risk of *Neisseria meningitides* serogroup A infection

Patients attending university for the first time (who have not received the routine meningococcal groups A with C and W135 and Y conjugate vaccine over the age of 10 years), By IM injection: **18–24 years:** 0.5 mL for 1 dose

Meningococcal group B vaccine (rDNA, component, adsorbed)

BEXSERO ®

Immunization against Neisseria meningitidis, primary immunization, By Deep IM injection:

Child 2 months: 0.5 mL for 1 dose, injected preferably into deltoid region (or anterolateral thigh in infants)

Child 4 months: 0.5 mL for 1 dose, injected preferably into deltoid region (or anterolateral thigh in infants)

Immunization against Neisseria meningitidis, primary immunization booster dose, By Deep IM injection:

Child 12–23 months: 0.5 mL for 1 dose, injected preferably into deltoid region (or anterolateral thigh in infants)

Immunization against Neisseria meningitidis, primary immunization (in unimmunized patients), By Deep IM injection:

Child 6–11 months: 0.5 mL for 2 doses, separated by an interval of at least 2 months; booster dose of 0.5mL given between 1–2 years of age and at least 2 months after completion of primary immunization, injected preferably into deltoid region (or anterolateral thigh in infants)

Child 12–23 months: 0.5 mL for 2 doses, separated by an interval of at least 2 months; booster dose of 0.5mL given 12–24 months after completion of primary immunization, injected preferably into deltoid region (or anterolateral thigh in infants)

Child 2–10 years: 0.5 mL for 2 doses, separated by an interval of at least 2 months. Injected preferably into deltoid region (or anterolateral thigh in infants)

Child 11–17 years: 0.5 mL for 2 doses, separated by an interval of at least 1 month. Injected preferably into deltoid region

TRUMENBA®

Immunization against Neisseria meningitidis, primary immunization, By Deep IM injection:

Child 10–17 years: 0.5 mL for 2 doses, separated by an interval of 6 months, alternatively 0.5 mL for 2 doses, separated by an interval of at least 1 month, followed by 0.5 mL as a third dose, given at least 4 months after the second dose, injected preferably into deltoid region, a booster dose should be considered for individuals at continued risk—consult product literature

Meningococcal Group C Vaccine

Patients with confirmed serogroup C disease (who have previously been immunized), By IM injection:

Child 1–17 years: 0.5 mL for 1 dose, dose to be given before discharge from hospital

Meningococcal Groups A With C And W135 And Y Vaccine

MENVEO®

Primary immunization against Neisseria meningitidis, By IM injection:

Child 13–15 years: 0.5 mL for 1 dose, dose preferably injected into deltoid region

immunization against Neisseria meningitidis in an unimmunized patient, By IM injection:

Child 10–17 years: 0.5 mL for 1 dose, booster dose is not required

immunization against Neisseria meningitidis in those at risk of exposure to prevent invasive disease, By IM injection:

Child 3–11 months: 0.5 mL every month for 2 doses

Child 1–17 years: 0.5 mL for 1 dose

Dose preferably injected into deltoid region

NIMENRIX®

Primary immunization against Neisseria meningitidis, By IM injection:

Child 13–15 years: 0.5 mL for 1 dose, to be injected preferably into deltoid region

immunization against Neisseria meningitidis in an unimmunized patient, By IM injection:

Child 10–17 years: 0.5 mL for 1 dose, booster dose is not required

Immunization against Neisseria meningitidis in those at risk of exposure, By IM injection:

Child 1–17 years: 0.5 mL for 1 dose, to be injected preferably into deltoid region (or anterolateral thigh in child 12–23 months), then 0.5 mL after 1 year if required for 1 dose, second dose should be considered in those who continue to be at risk of *Neisseria meningitidis* serogroup A infection

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Acute illness: postpone all vaccinations until patient is well.

Adverse effects: Common: Meningococcal C vaccine: irritability, anorexia, headache.

Both vaccines: transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare: Allergic reactions including anaphylaxis.

Interaction with other medicines: There are no known interactions where it is recommended to avoid concomitant use.

Notes:

- Injection is a capsular polysaccharide antigen of Neisseria meningitidis serogroup C conjugated to a protein carrier and adsorbed onto a mineral carrier, and the same for serogroups A and C or groups A, C, W135 and Y
- The polysaccharide versions of this vaccine are recommended to control outbreaks and for at-risk individuals including travelers to endemic areas. The unconjugated versions of this vaccine elicit a suboptimal response in infants under 2 years of age and are not recommended for routine immunization, however, they may be given in emergency outbreak situations.
- *N. meningitidis* causes meningococcal disease including meningitis and septicaemia and primarily affects young children. The bacteria are transmitted from person to person via respiratory secretions. Immunization against meningococcal disease is recommended as part of the routine childhood immunization programme, for outbreak situations, for individuals at high risk including those in military camps and boarding schools, travelers to endemic areas, and for those with a predisposition to meningococcal disease (such as asplenia and inherited immune deficiencies).
- Meningococcal vaccines are available as combinations of capsular polysaccharide antigens (serogroups A and C, or A, C, W135 and Y) or as a polysaccharide of serogroup C conjugated to a protein carrier. There is also a polysaccharide of serogroups A, C, Y and W135 conjugated to a protein carrier. Other variants of the vaccine are available in some countries.
- Group C conjugate vaccine is recommended for national childhood immunization programmes, for children 2–12 months of age, three doses are given at intervals of 4 weeks. A booster at 12 months is recommended.
- A single dose of group C conjugate vaccine is sufficient in children over 12 months of age. However, individuals with asplenia or splenic dysfunction should be given two doses each 2 months apart, immunized individuals who develop splenic dysfunction should be given one additional dose.
- A single dose of either A and C, or A, C, W135 and Y polysaccharide vaccine is recommended to control outbreaks and for at-risk individuals including travelers to endemic areas. Groups A and C, and A, C, W135 and Y unconjugated vaccines elicit a suboptimal response in infants under 2 years of age and are not recommended for routine immunization, however, they may be given in emergency outbreak situations.
- Meningococcal C conjugate vaccines is also known as MenCCV.
- Meningococcal polysaccharide vaccines (groups A, C, Y and W135) also known as 4vMenPV.
- Meningococcal conjugate vaccine (groups A, C, Y and W135) also known as MCV4.

Rabies Vaccine (Cell Culture)

ATC code: J07BG01

Injection, Single dose (Purified Vero cell/ human diploid), LOU 2

Indications and dose

Adult

Pre-exposure prophylaxis against rabies, by IM injection: 3 doses on days 0, 7, and 28 (day 28 preferable, but administration may be advanced toward day 21 if time is limited);

Pre-exposure prophylaxis against rabies, by intradermal injection, 3 doses, each of 0.1 mL on days 0, 7, and 28 (administration may be advanced toward day 21 if time is limited)

Periodic **booster doses** are recommended only for individuals whose occupation puts them at continuous or frequent risk of rabies exposure. In such cases, a booster dose should be given at intervals dictated by regular testing for rabies antibodies (a concentration of virus neutralizing antibodies of at least 0.5 IU/mL indicates protection). When serological testing is unavailable, booster vaccination every 5 years may be an acceptable alternative.

Post-exposure treatment against rabies in unimmunized individuals, by IM injection: 1 dose given on days 0, 3, 7, 14, and 28 (total of 5 doses); alternatively, 2 doses on day 0 (one in each deltoid or thigh), followed by 1 dose on days 7 and 21 (total of 4 doses)

Post-exposure treatment against rabies in unimmunized individuals, by intradermal injection, 8-site regimen: 1 dose of 0.1 mL administered at 8 separate sites on day 0 (one in each upper arm, one in each lateral thigh, one on each side of the suprascapular region, and one on each side of the lower quadrant region of the abdomen), followed by 1 dose of 0.1 mL in each upper arm and each lateral thigh on day 7, and 1 dose of 0.1 mL in one upper arm on days 30 and 90; alternatively, a 2-site regimen of 1 dose of 0.1 mL at 2 sites on days 0, 3, 7, and 28 (total of 8 doses).

Post-exposure treatment against rabies in fully immunized individuals, by IM or intradermal injection: 2 doses, separated by 3 days

Paediatric

Pre-exposure immunization against rabies, IM

Child all ages: 1 mL on days 0, 7, and 28 (day 28 preferable, but administration may be advanced toward day 21 if time is limited).

Pre-exposure immunization against rabies, intradermal

Child all ages: 0.1 mL on days 0, 7, and 28 (administration may be advanced toward day 21 if time is limited)

Periodic **booster doses** are recommended only for individuals whose environment puts them at continuous or frequent risk of rabies exposure. In such cases, a booster dose should be given at intervals dictated by regular testing for rabies antibodies (virus neutralizing antibodies of at least 0.5 IU/mL indicate protection). Where serological testing is unavailable, booster vaccination every 5 years may be an acceptable alternative.

Post-exposure prophylaxis against rabies in unimmunized individuals, IM

Child all ages: 1 mL on days 0, 3, 7, 14, and 28 (five-dose regimen); alternatively, a four-dose regimen may be used with two doses of 1 mL on day 0 (one in each of the two deltoid or thigh regions) followed by one dose each on days 7 and 21.

Post-exposure prophylaxis against rabies in unimmunized individuals, intradermal

Child all ages (eight-site regimen): 0.1 mL administered at eight separate sites on day 0 (one in each upper arm, one in each lateral thigh, one on each side of the suprascapular region, and one on each side of the lower quadrant region of the abdomen); on day 7, 0.1 mL in each upper arm and each lateral thigh; on days 30 and 90, 0.1 mL in one upper arm; the one dose on day 90 may be replaced by two intradermal injections on day 30; alternatively (two-site regimen) 0.1 mL at two sites on days 0, 3, 7, and 28

Post-exposure treatment against rabies in fully immunized individuals, IM or intradermal

Child all ages: Two doses (1 mL IM or 0.1 mL intradermal) on days 0 and 3.

Contraindications: There are no contraindications to post-exposure prophylaxis following high-risk exposure. For pre-exposure immunization, previous severe reaction to any of the vaccine components is a contraindication to further use of the same vaccine.

Precautions: Concomitant chloroquine use (reduced response to intradermal route, use IM route), concomitant rabies immunoglobulin (administer using different sites and different syringes).

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Common: Headache, dizziness, malaise, myalgia, nausea, serum sickness-like reaction (after booster dose), weakness, rash, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting, mild GI disturbances.

Angioedema.

Rare: Neuroparalytic events, allergic reactions including anaphylaxis.

Interaction with other medicines:

There are no known interactions where it is recommended to avoid concomitant use.

Notes:

- WHO recommends the intradermal route of administration for rabies pre- and post-exposure prophylaxis. Refer to manufacturer literature for product specific advice.
- Intradermal administration is technically more demanding and requires appropriate staff training and qualified supervision.
- Rabies is a virus transmitted to humans by rabid animals via a bite or scratch. It is invariably fatal once signs of disease occur. WHO recommends pre-exposure immunization of individuals at increased risk of contracting rabies either due to occupational exposure such as laboratory workers, veterinary surgeons, animal handlers and health workers or people living or travelling to enzootic areas, in such areas children aged 5–15 years are at particular risk of exposure. Cell-derived vaccines are used for both pre-exposure and post-exposure protection. Vaccines of nerve cell tissue origin should not be used because they are less potent and are frequently associated with adverse events.
- Rabies vaccine is used as part of the post-exposure treatment to prevent rabies in patients who have been bitten by rabid animals or animals suspected of being rabid. The bite wound or scratch should be thoroughly cleansed. Treatment is dependent upon the individual's immune status and upon the level of risk of rabies in the country concerned (consult national immunization schedule).
- In certain circumstances, such as patients with incomplete prophylaxis or unimmunized individuals, passive immunization with rabies immunoglobulin can be given. Rabies has occurred in people who have received post-exposure rabies vaccine without rabies immunoglobulin being infiltrated in and around the wound. Therefore, post-exposure treatment, in those who have not completed pre-exposure prophylaxis, should include infiltration of human rabies immunogobulin in and around wound(s) at the same time as the first dose of the rabies vaccine.
- Post-exposure treatment with rabies vaccine and rabies immunoglobulin is necessary for individuals who are immunocompromised, HIV-positive, taking malaria chemoprophylaxis or under anaesthesia, antibody response should be monitored.

Typhoid Vaccine

ATC code: J07AP01, J07AP03

Injection (solution), single or multidose, LOU 2

IM or SC using Vi-based polysaccharide parenteral vaccine

Indications and dose

Vaccination of children under 2 years and those at highest risk of contracting or transmitting the disease (food handlers, especially those employed in institutions and hotels, laboratory staff, and employees

of sewage and treatment works) should be prioritized.

Adult

Active immunization against typhoid, IM or SC: Single dose, followed by booster doses every 3 years on continued exposure

Paediatric

Immunization against S. typhi fever, IM or SC

Child 2 years and over: Single dose, followed by booster doses every 3 years on continued exposure

Contraindications: Anaphylaxis following previous typhoid vaccine or history of anaphylaxis to one of the vaccine components, acute GI illness (oral vaccine).

Precautions: Acute illness (postpone vaccination until well), HIV-positive patients, immunosuppressed patients, treatment with anti-infectives active against *S. typhi*.

HIV and immunosuppressed patients Asymptomatic HIV-positive individuals can be given the vaccine if CD4 counts are over 200 cells/mm3. It is recommended to use the Vi-based polysaccharide parenteral vaccine rather than the oral vaccine in individuals with impaired immunity.

Oral typhoid vaccine is inactivated by concomitant administration of antibacterials, if possible, antibacterials should be avoided 3 days before and 3 days after.

Hepatic impairment: No dose reduction required.

Renal impairment: No dose reduction required.

Adverse effects: Common: IM vaccine: headache, nausea, malaise, myalgia.

Oral vaccine: diarrhoea, constipation, nausea, vomiting, anorexia.

Rare: Allergic reaction.

Interaction with other medicines (*indicates serious):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* Azathioprine: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* Ciclosporin: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* Dexamethasone: high doses of dexamethasone impair immune response, avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* Hydrocortisone: high doses of hydrocortisone impair immune response, avoid use of live vaccines.

Mefloquine: recommend a 12 hour interval between mefloquine and doses of oral typhoid vaccine, vaccination should be completed at least 3 days before the first dose of mefloquine.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* Prednisolone: high doses of prednisolone impair immune response, avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Proguanil: unless combined with atovaquone, start proguanil at least 10 days after the last oral typhoid vaccine dose (or use IM vaccine).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes:

- Typhoid fever is caused by *Salmonella typhi*. It is transmitted via the faecal-oral route and associated with poor hygiene and sanitation. Immunization against typhoid fever is recommended for children of school age and adults in endemic areas, travelers to endemic areas and laboratory workers handling specimens from suspected cases. The vaccines do not provide complete protection and should not replace hygiene precautions.
- A single dose of parenteral Vi capsular polysaccharide vaccine is recommended for adults and children over 2 years of age, followed by booster doses every 3 years on continued exposure.
- A live oral typhoid vaccine containing an attenuated strain of *S. typhi* (Ty21a) is available either as enteric-coated capsules, or as a liquid suspension. The capsules are licensed for individuals over 5 years of age and are given as four doses, each 2 days apart, the suspension can be administered to children over 2 years of age and is given as three doses, each 2 days apart. Protection is achieved 7 days after the last dose. In endemic areas, a booster dose of the live oral vaccine is recommended every 3 years, for travelers to endemic areas from non-endemic areas, an annual booster is recommended.
- Inactivated whole cell typhoid vaccines may still be available in some countries, children over 5 years of age are given two doses separated by an interval of 4 weeks, with a booster dose every 3 years. However, inactivated whole cell vaccines are associated with frequent adverse

effects and WHO recommends that these vaccines should be replaced with either the Vi-based polysaccharide vaccine or live oral vaccines.

21.3.4. Recommended For Immunisation Programmes With Certain Characteristics

Influenza Vaccine (Inactivated)

ATC code: J07BB

Injection, 0.5-mL vial (single dose) - LOU 2

Indications and dose

Adult

Immunization against influenza (annually for high-risk persons), *by IM injection:* 0.5 mL as a single dose

Paediatric

Immunization against influenza (annually for high-risk persons), by IM injection:

Infant or **child 6 months–3 years:** 0.25 mL (one or two doses)

Child over 3 years: 0.5 mL (one or two doses)

Child over 9 years: 0.5 mL as a single dose

Contraindications: Hypersensitivity to influenza virus vaccine or any component, allergy to egg or egg products, chicken, chicken feathers or chicken dander, presence of acute respiratory disease or other active infections or illnesses (delay immunization), influenza vaccines from previous seasons must not be used.

Precautions: History of febrile convulsions or Guillain-Barré syndrome, children < 5 years (adverse effects may be more severe), acute febrile illness (postpone all vaccinations until patient is well).

Hepatic impairment: No dose reduction necessary.

Renal impairment: No dose reduction necessary.

Adverse effects: Common: Fever, malaise, myalgia, headache (these reactions may last 1–2 days), transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare: Allergic reactions (hives, angioedema, asthma, anaphylaxis).

Interaction with other medicines (*indicates serious):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* Azathioprine: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* Ciclosporin: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* Dexamethasone: high doses of dexamethasone impair immune response, avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* Hydrocortisone: high doses of hydrocortisone impair immune response, avoid use of live vaccines.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* Prednisolone: high doses of prednisolone impair immune response, avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes:

- A second dose after at least 4 weeks is recommended in previously unvaccinated children 6 months to 9 years of age.
- Influenza viruses type A and B are common causes of respiratory illnesses and are transmitted from person to person via droplets or respiratory secretions, their antigenic structure is constantly changing. WHO monitors these changes each year and makes recommendations for inclusion of strains in the influenza vaccines for the following season.
- There are various forms of inactivated influenza vaccine available, and live vaccines are licensed for use in some countries. Some vaccines are grown on chick embryos and are therefore contraindicated in individuals hypersensitive to eggs. Split virus vaccines and subunit vaccines show reduced systemic reactogenicity compared with whole virus preparations.
- Annual immunization with inactivated vaccine is recommended in patients of any age with diabetes mellitus, chronic heart disease, chronic liver disease, chronic renal disease, chronic respiratory disease including asthma, or immunosuppression due to disease or drug treatment. Vaccination with inactivated vaccine can be considered for contacts of high-risk people, children between 6–23 months of age, health-care workers or other key workers, on the basis of national risk.

22. Ophthalmological Preparations

22.1. Anti-Infective Agents

Acyclovir

ATC code: S01AD03

Eye ointment, 3% w/w, LOU 4

Indications and dose

Adult

Keratitis caused by herpes simplex: 1 cm of ointment 5 times daily in the affected eye(s); continue for at least 3 days after healing is complete.

Paediatric

Herpes simplex keratitis, eye

Infant or **child:** 1 cm of ointment five times daily in the affected eye(s), continue for at least 3 days after healing is complete.

Precautions: Wearing contact lenses should be avoided when using acyclovir ophthalmic ointment.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Common: Local irritation including transient mild stinging, inflammation.

Superficial punctate keratopathy.

Rare: Blepharitis, hypersensitivity reactions including angioedema.

Interaction with other medicines

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

» Avoid contaminating the tip of the ointment tube.

Dexamethasone + Polymixin B Sulfate + Neomycin Sulfate

ATC code: R01AD53

Ointment, 1mg Dexamethasone, 6000 IU polymixin B sulfate, 3500 IU Neomycin sulfate, LOU 4

Indications and dose

Adult

Post-operative after cataract surgery, allergic conjunctivitis, Local treatment of inflammation, ocular use: apply 3-4 times a day. Alternatively, apply at night when used with eye drops.

Paediatrics

Same as adults

Contraindications: Hypersensitivity to the active substances or to any of the excipients, Herpes simplex keratitis, Vaccinia, varicella, and other viral infection of cornea or conjunctiva, Fungal diseases of ocular structures or untreated parasitic eye infections, Mycobacterial ocular infections.

Precautions: prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi, Cross-sensitivity to other aminoglycosides may occur, hypersensitivity reactions, risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes), Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ocular dexamethasone may occur after intensive or long-term continuous therapy, In diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids, topical ophthalmic corticosteroids may slow corneal wound healing.

Pregnancy: not recommended during pregnancy.

Adverse effects: Prolonged use of ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity and visual field defects, and posterior subcapsular cataract formation, Visual disturbance.

Interactions with other medicines (*indicates serious): *neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic neomycin or when applied topically to open wounds or damaged skin. Nephrotoxic and neurotoxic reactions have also occurred with systemic polymyxin B, Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems, CYP3A4 inhibitors may decrease dexamethasone clearance resulting in increased effects and adrenal suppression/Cushing's syndrome, Concomitant and/or sequential use of an aminoglycoside (neomycin) and other systemic, oral, or topical drugs that have neurotoxic, ototoxic, or nephrotoxic effects may result in additive toxicity

Erythromycin

ATC code: S01AA17

Eye ointment, 0.5%, LOU 4

Indications and dose

Adult

Topical treatment of superficial ocular infections of the conjunctiva and/or cornea caused by susceptible organisms: Apply a thin strip (approximately 1 cm) in the affected eye(s) 6 times a day.

Paediatric

Topical prophylaxis of neonatal conjunctivitis caused by Chlamydia trachomatis, topical treatment of superficial ocular infections of the conjunctiva and/or cornea caused by susceptible organisms, to each conjunctiva,

Infant: apply a thin strip (approximately 0.5 to 1 cm) of ointment as a single dose in both eyes following cesarean or vaginal delivery

Topical treatment of superficial ocular infections of the conjunctiva and/or cornea caused by susceptible organisms:

Child: Apply a thin strip (approximately 1 cm) in the affected eye(s) 6 times a day

Contraindications: Hypersensitivity to erythromycin products

Precautions: intolerance to erythromycin.

Adverse effects: eye irritation.

Gentamicin

ATC code: S01AA11

Solution (eye drops),0.3% (sulphate), LOU 2

Indications and dose

Adult

Blepharitis, bacterial conjunctivitis, mild to moderate infection, by ocular instillation: 1 drop in the affected eye(s) every 2 hours, reducing frequency as infection is controlled, then continue for 48 hours after healing is complete.

Blepharitis, bacterial conjunctivitis, severe infection, by ocular instillation: 1 drop in the affected eye(s) every hour, reducing frequency as infection is controlled, then continue for 48 hours after healing is complete.

Paediatric

Blepharitis, bacterial conjunctivitis, mild to moderate infection

Infant or **child:** 1 drop in the affected eye(s) every 2 hours, reducing frequency as infection is controlled to 1 drop four times daily, and then continued for 48 hours after healing is complete.

Blepharitis, bacterial conjunctivitis, severe infection

Infant or **child:** 1 drop in the affected eye(s) every hour, reducing frequency as infection is controlled to 1 drop four times daily, and then continued for 48 hours after healing is complete.

Contraindications: Hypersensitivity to aminoglycoside group of antibiotics.

Precautions: Prolonged use may lead to skin sensitization and emergence of resistant organisms including fungi, discontinue if purulent discharge, inflammation or exacerbation of pain.

Adverse effects: Common: Burning, stinging, itching, dermatitis, redness, lacrimation, superficial punctate keratitis.

Delayed corneal epithelial wound healing, retinal toxicity (if there is leakage through corneoscleral wound).

Rare: Hypersensitivity reactions.

Interaction with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

Avoid contaminating the tip of the solution bottle.

Apply finger pressure to the lacrimal sac during and for 1–2 minutes after instillation to decrease risk of absorption and systemic effects.

Gentamicin + Dexamethasone

ATC code: S01CA01

Eye drops, 0.3% + 0.1%, LOU 4

Indications and dose

Adult

Mild to moderate bacterial conjunctivitis and eyelids associated with inflammation, pre- and post-operatively for prevention of infection and scarification.

Instill one to two drops in the affected eye four times daily.

Paediatric

Mild to moderate bacterial conjunctivitis and eyelids associated with inflammation, pre- and post-operatively for prevention of infection and scarification.

Instill one to two drops in the affected eye four times daily.

Contraindications: Hypersensitivity to aminoglycoside group of antibiotics or corticosteroids, viral infections of the cornea and conjunctiva, fungal infection of ocular structures

Precautions: use in patient with history of herpes simplex, long term use can lead to corneal and scleral thinning, glaucoma

Adverse effects: Common: Hypersensitivity reactions, burning, stinging, itching, dermatitis, redness, lacrimation, superficial punctate keratitis.

Delayed corneal epithelial wound healing, retinal toxicity (if there is leakage through corneoscleral wound).

Moxifloxacin

ATC code: S01AE07

Eye drops, 0.5% w/v (as HCL) 5ml, LOU 5

Indications and dose

Adult

Used to treat *infections of the eye, including bacterial conjunctivitis*, *Apply:* 3 times a day for 2–3 days after infection improves; review if no improvement after 5 days

Paediatric

Not recommended for neonates

No dosage adjustment required for paediatrics.

Contraindications: Hypersensitivity to the active substance, to other quinolones, or to any of the excipients

Precautions: occasionally fatal hypersensitivity (anaphylactic) reactions, Tendon inflammation and rupture may occur.

Hepatic impairment: No dosage adjustment is necessary.

Renal impairment: No dosage adjustment is necessary.

Adverse effects: Conjunctival haemorrhage, acute hypersensitivity reactions.

Natamycin

ATC code: S01AA10

Eye drops, 5%, LOU 5

Indications and dose

Adult

Conjunctivitis and fungal blepharitis, fungal keratitis: Instill 1 drop every 1 – 2 hours, reduced to 6–8 times daily after 3–4 days, and generally continued for 14–21 days.

Paediatric

Conjunctivitis and fungal blepharitis, fungal keratitis:

Child: Instill 1 drop every 1 – 2 hours, reduced to 6–8 times daily after 3–4 days, and generally continued for 14–21 days

Contraindications: hypersensitivity to the drug.

Precautions: concurrent application of natamycin and a topical corticosteroid.

Adverse effects: eye irritation, redness, or swelling.

Note: Patient should not wear contact lenses until infection resolves

Ofloxacin

ATC Code: S02AA16

Eye drops, 0.3% (as sulphate), LOU 4

Indications and dose

Adult

Conjunctivitis: Instill 1–2 drops in affected eye(s) every 2–4 hours for the first 2 days, then use 4 times/day for additional 5 days

Corneal ulcer: 1–2 drops every 30 minutes while awake and every 4–6 hours after retiring for the first 2 days; beginning on day 3, instill 1–2 drops every hour while awake for 4–6 additional days; thereafter, 1–2 drops 4 times/day until clinical cure.

Paediatric

Conjunctivitis,

Child>1 year: Instill 1–2 drops in affected eye(s) every 2–4 hours for the first 2 days, then use 4 times/day for additional 5 days.

Corneal ulcer:

Child>1 year: 1–2 drops every 30 minutes while awake and every 4–6 hours after retiring for the first 2 days; beginning on day 3, instill 1–2 drops every hour while awake for 4–6 additional days; thereafter, 1–2 drops 4 times/day until clinical cure.

Contraindications: History of hypersensitivity to Ofloxacin, to other quinolone, or to any of the components in this medication

Adverse effects: dizziness, nausea, blurred vision, burning, discomfort in the eye, edema, eye pain, redness, stinging, tearing.

Ofloxacin + Dexamethasone

ATC code: S01CA01

Eye drops, 0.3% + 0.1%, LOU4

For details refer to individual monographs for Ofloxacin (22.1) and Dexamethasone (22.2)

Tetracycline

ATC code: S01AA09

Eye ointment, 1% (HCl), LOU 1

Superficial bacterial infection of the eye, mass treatment of trachoma in endemic areas, prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to *Neisseria gonorrhoea* or *Chlamydia trachomatis*

Indications and dose

Adult

Superficial bacterial infection:

1 application of ointment directly to the eye 3–4 times daily

Trachoma, intermittent treatment: 1 application of ointment directly into each eye either twice daily for 5 days or once daily for 10 days, every month for 6 consecutive months each year, repeated as necessary.

Trachoma, continuous intensive treatment: 1 application of ointment directly into each eye twice daily for at least 6 weeks

Paediatric

Prophylaxis of neonatal conjunctivitis, eye

Neonate at birth: As soon as possible after delivery after cleansing eyes with sterile gauze, one application of ointment into each eye; close eyelids and massage gently to aid spread of ointment.

Superficial bacterial infection, eye

Infant or **child:** 1 application of ointment 3–4 times daily

Trachoma, intermittent treatment, eye

Infant or **child:** 1 application of ointment into each eye either twice daily for 5 days or once daily for 10 days, every month for 6 consecutive months each year, repeated as necessary.

Trachoma, continuous intensive treatment, eye

Infant or **child:** 1 application of ointment into each eye twice daily for at least 6 weeks

Contraindications: Hypersensitivity to tetracycline group of antibiotics, photodermatosis.

Precautions: Prolonged use may lead to overgrowth of non-susceptible organisms, intensive exposure to the sun or ultraviolet radiation should be avoided during treatment since photodermatosis has been observed in isolated cases in hypersensitive patients.

Adverse effects: Rare: Rash, stinging, burning, allergic reaction, photodermatosis.

Interaction with other medicines

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

» Avoid contaminating the tip of the ointment tube. When treating bacterial conjunctivitis, it is advisable to continue therapy for a further 2–3 days after regression of the symptoms.

Tobramycin

ATC code: S01AA12

Eye Drops, 0.3% (as sulphate) 5ml, LOU 3

Indications and dose

Adult

Treatment of external infections of the eye and its adnexa caused by susceptible bacterial:

Apply twice daily for 6–8 days Severe infection: Apply 4 times a day for first day, then apply twice daily for 5–7 days.

Paediatric

Neonate: Safety and effectiveness in patients below two months have not been established.

Child 1–17 years: *Simple infections:* Apply twice daily for 6–8 days. *Severe infection*: Apply 4 times a day for first day, then apply twice daily for 5–7 days.

Contraindications: Contraindicated in patients with known hypersensitivity to any of its components

Precautions: Sensitivity to topically administered aminoglycosides may occur

Pregnancy: Should be used during pregnancy only if clearly needed

Breastfeeding: Because of potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing infant or discontinue drug, taking into account importance of drug to mother

Adverse effects: Hypersensitivity and localized ocular toxicity, including lid itching and swelling and conjunctival erythema.

Tobramycin + Dexamethasone

ATC code: S01CA01

Eye Drops, 0.3% + 0.1%, 5ml, LOU 4

Indications and dose

Adult

Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults and children aged 2 years and older, ocular use: One drop instilled into the conjunctival sac(s) every 4 to 6 hours while the patient is awake. Dosing should continue for 14 days to a maximum of 24 days.

Paediatric

Older than 2 years: *One drop instilled into the conjunctival sac(s) every 4 to 6 hours while the patient is awake. Dosing should continue for 14 days to a maximum of 24 days.*

Contraindications: Hypersensitivity to tobramycin or dexamethasone or to any of the excipients, Herpes simplex keratitis, Viral disease of the cornea and conjunctiva, Mycobacterial infections of the eye, Fungal diseases or untreated parasitic eye infection

Precautions: Prolonged use of topical ophthalmic corticosteroids than recommended may result in ocular hypertension/glaucoma with resultant damage to the optic nerve, reduced visual acuity and visual fields defects

Pregnancy: Not recommended during pregnancy

Breastfeeding: Need to assess the benefit of breast feeding for the child and the benefit of therapy for the woman.

Adverse effects: Eye irritation, ocular hyperaemia, erythema of eyelid, abnormal sensation in eye, eye pruritus, ocular discomfort, eye allergy, eyelid oedema, conjunctivitis, glare, increased lacrimation, keratitis

Interactions with other medicines (*indicates serious): Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.

Voriconazole

ATC Code: Not Assigned

Powder for eye-drops (Sterile Lyophylized powder), 1% w/v, LOU5

Indications and Dose:

Adult and Paediatric

Refractory Fungal Keratitis, Specialist use

Adverse effects: Eye irritation, Burning sensation, Blurred vision.

Notes:

» *The reconstituted eye drops are stable for 30 days.*

22.2. Anti-Inflammatory Agents

Dexamethasone

ATC code: S01BA01

Eye Drops, 0.1%, 5ml, LOU 4

Indications and dose

Adult

Inflammatory conditions of the anterior segment of the eye, e.g. marginal keratitis, stromal oedema in keratitis, anterior uveitis, iritis, cyclitis, allergic and vernal conjunctivitis, herpes zoster keratitis, superficial punctate keratitis and non-specific superficial keratitis, Ocular use; Severe: Apply one drop in to the eye every 30–60 minutes until controlled, reduce frequency to one drop every 4 hours. Moderate: Adult: Apply 4–6 times a day.

Paediatric

Safety and efficacy of this product has not been established in children below 2 years of age

Contraindications: Hypersensitivity to the active substance or to any of the excipients, in herpes simplex and other viral diseases of the cornea and conjunctiva, fungal disease, ocular tuberculosis

Precautions: With intravitreal use - History of ocular viral infection (including herpes simplex), posterior capsule tear or iris defect (risk of implant migration into the anterior chamber which may cause corneal oedema and, in persistent severe cases, the need for corneal transplantation), retinal vein occlusion with significant retinal ischaemia.

Pregnancy: Avoid unless potential benefit outweighs risk.

Breastfeeding: Avoid unless potential benefit outweighs risk.

Adverse effects: Risk of corneal deposits or corneal opacity, eye discomfort, photo phobia

Interactions with other medicines (*indicates serious): Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems, CYP3A4 inhibitors may decrease dexamethasone clearance resulting in increased effects and adrenal suppression/Cushing's syndrome.

Fluorometholone

ATC code: S01BA07

Eye drops, 0.1%, LOU 3

Indications and dose

Adult

Corticosteroid-responsive allergic conjunctivitis; active inflammation of conjunctiva, cornea, and anterior segment of the globe; prevention or treatment of complications, such as cystoid macular oedema; corneal allograft rejection; explosive onset of severe noninfectious posterior uveitis; panuveitis or optic neuritis

Severe inflammation: Instill 1 drop every hour during day, every 2 hours at night until favorable response is obtained, then taper to 1 drop every 4 hours

Mild to moderate inflammation: Instill one drop 2–4 times/day

Paediatric

Corticosteroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

Child > 2 years old: 1 drop into the conjunctival sac 2 to 4 times per day

Contraindications: Patients with ocular fungal diseases, herpes simplex keratitis, TB, viral disease, cataracts, open angle glaucoma

Precautions: Long-term use of corticosteroid need close follow-up for glaucoma (open-angle glaucoma) and for other major complications. Corticosteroid therapies, longer than 2–3 weeks, should be tapered before discontinuation. All corticosteroids may exacerbate bacterial, viral, mycobacterial and fungal diseases of the eye and should be used with caution in these settings.

Adverse effects: Glaucoma, cataract formation, secondary ocular infections or exacerbations of ocular infections are the most serious ocular Adverse effects. Other ocular Adverse effects include decreased vision, lacrimation, burning, stinging, redness, optic nerve damage, eye pain and ptosis.

Interaction with other medicines Desmopressin

Note:

Advise patient to report symptoms of an eye infection. Counsel patient to consult doctor if eye pain or inflammation is aggravated or persists beyond 48 hours after therapy begins. Patient should report symptoms of elevated intraocular pressure (e. g eye pain, regional headache, lacrimation, visual halos) or vision changes as soon as they occur.

Ketorolac trometamol

ATC code: S01BC05

Eye drops, 0.5%, LOU 4

Indications and dose

Adult

Allergic conjunctivitis: Instill 1 drop in the affected eye(s) every 6 hours

Inflammation following cataract extraction: Instill 1 drop every six hours in the affected eye(s) for 2 weeks, beginning 24 hours after surgery

Eye pain, burning, or stinging following corneal refractive surgery: Instill one drop in the affected eye(s) 4 times a day for up to 4 days after the surgery.

Paediatric

Allergic conjunctivitis:

Child≥2 years old: Instill 1 drop in the affected eye(s) every 6 hours

Inflammation following cataract extraction:

Child≥2 years old: Instill 1 drop every six hours in the affected eye(s) for 2 weeks, beginning 24 hours after surgery

Eye pain, burning, or stinging following corneal refractive surgery:

Child≥3 years old: Instill one drop in the affected eye(s) 4 times a day for up to 4 days after the surgery.

Contraindications: hypersensitivity to ketorolac or other systemic or ophthalmic NSAIMs

Precautions: Patients with known bleeding tendencies or those receiving anticoagulants, paediatric patients<3 years of age

Adverse effects: transient burning/stinging, headache, conjunctival hyperemia, corneal infiltrates, iritis, ocular edema, superficial keratitis.

Note:

Advise patient to remove contact lenses prior to instilling drug

Methylprednisolone

ATC code: S01CA08

Powder for injection, 1g vial (as sodium succinate), LOU 5

Indications and dose:

Adult

vision-threatening, explosive onset of severe non-infectious posterior uveitis, panuveitis or optic neuritis, iv infusion:

methylprednisolone (1 gm/day infused over 1 hour) therapy may be administered for 3 days, followed by oral prednisone starting at 1–2 mg/kg/day, which is tapered in a gradual fashion every 1 to 2 weeks until the disease is quiescent. The lowest possible dose that will control the ocular inflammation and minimize adverse effects is desired. This dose should be 5–10 mg or less per day

Paediatric

vision-threatening, explosive onset of severe non-infectious posterior uveitis, panuveitis or optic neuritis, iv infusion:

Infants and child <12 years: 1 to 2 mg/kg/day in 1 or 2 divided doses, maximum daily dose: 60mg/day

Child> 12years: 1 gm/day infused over 1 hour

Contraindications: Patients with ocular fungal diseases, herpes simplex keratitis, TB, viral disease, cataracts, open angle glaucoma, diabetes mellitus, hypertension, peptic ulcer or GERD, patients who are immunocompromised (from acquired or congenital causes) and patients with psychiatric conditions are at high risk for corticosteroid-induced exacerbations of their systemic conditions. In these patients, Corticosteroids treatment should be avoided or used as the last choice.

Precautions: Long-term use of corticosteroid need close follow-up for glaucoma (open-angle glaucoma) and for other major complications. Corticosteroid therapies, longer than 2–3 weeks, should be tapered before discontinuation. All corticosteroids may exacerbate bacterial, viral, mycobacterial and fungal diseases of the eye and should be used with caution in these settings.

Adverse effects: Glaucoma, cataract formation, secondary ocular infections or exacerbations of ocular infections are the most serious ocular Adverse effects. Retardation of skeletal maturation and growth, osteoporosis and bone fractures, cushingoid appearance, diabetes, peptic ulcers, myopathy, hypertension, altered mental status, pseudotumor cerebri, and Addisonian crisis on withdrawal.

Interaction with other medicines:

Desmopressin, rotavirus vaccine, aceclofenac, besifloxacin, gatifloxacin, norfloxacin, ofloxacin, aspirin, atracurium, carbamazepine, clarithromycin, cyclosporine, diltiazem, erythromycin, fluindione, ketoconazole, licorice, phenobarbital, primidone, rifampin, warfarin

Prednisolone

ATC code: S01BA04

Eye drops, 1% (as acetate) (5 mL), LOU 4

Indications and dose

Adult

Short-term local treatment of inflammation of the eye, including severe allergic conjunctivitis, iritis, and uveitis, and following intraocular surgery, by ocular instillation: 1 drop every 1–2 hours, reducing frequency as inflammation is controlled

Paediatric

Inflammation of the eye

Neonate, infant, or **child:** 1 drop every 1–2 hours, reducing frequency as inflammation is controlled

Contraindications: Undiagnosed 'red eye' caused by herpetic keratitis, glaucoma.

Precautions: Cataract, corneal thinning, corneal or conjunctival infection, discontinue treatment if no improvement within 7 days, risk of adrenal suppression after prolonged use in infants, allergy to sodium bisulfite which may be contained in ophthalmic solution.

Adverse effects: Common: Ocular hypertension (usually reversible and is proportional to dose, potency, penetration and duration of treatment), retarded corneal healing due to corneal thinning, rebound inflammation.

Secondary ocular infection, mydriasis, epithelial punctuate keratitis.

Rare: Transient stinging, burning or local irritation, refractive changes, ptosis, chemosis, lid swelling, exophthalmos (slowly, incompletely reversible), with prolonged use: optic nerve damage, defects in visual acuity and field of vision, open-angle glaucoma and cataracts. Posterior subcapsular cataracts may occur with long-term (> 1 year) high-dose use, mostly asymptomatic and partially reversible.

Interaction with other medicines:

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

Avoid contaminating the tip of the solution bottle. Apply finger pressure to the lacrimal sac during and for 1–2 minutes after installation to decrease risk of absorption and systemic effects. Use only under the supervision of an ophthalmologist.

Triamcinolone

ATC code: S01BA05

Injection, (aq. Suspension as acetonide) 40 mg/1-mL amp, LOU 5

Indications and dose

Adult

Suppression of inflammatory and allergic disorders, posterior uveitis, macular oedema, deep IM injection, into gluteal muscle: 40 mg of acetonide for depot effect, repeated at intervals according to the patient's response, maximum single dose 100 mg

Intracameral: 40 mg

Intravetrial injection: 40 mg

Subtenon injection: 20 mg

Supratarsal injection: 20 mg

Paediatric

Follow adult dosing

Contraindications: concomitant administration of live or live attenuated vaccines, hypersensitivity to triamcinolone acetonide or any other component of the product, IM injection for idiopathic thrombocytopenic purpura and primary treatment for status asthmaticus or acute asthma.

Precautions: High dose may cause proximal myopathy, avoid in chronic therapy. Increased risk of secondary ocular infection, cataracts and glaucoma.

Adverse effects: Anorexia, weight loss, flushing, depression, and muscle wasting are reported to have been particularly associated with Triamicinolone.

Interaction with other medicines

Desmopressin, rotavirus vaccine, besifloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, aspirin, atracurium, fosphenytoin, licorice, phenytoin, ritonavir

Note:

Advice patient to avoid vaccines during therapy unless approved by a health care professional.

22.3. Local Anaesthetics

Lignocaine/ Lidocaine

ATC code: S01HA07

Eye Drops, 2% (as HCL), LOU 4

Indications and dose

Adult

A local anaesthetic for ophthalmic installation. Used to numb the eye before surgery, certain tests, or procedures: 2 drops ONCE, applied to the ocular surface where the procedure is planned

Paediatric

Safety and efficacy of this formulation have not been established in pediatric patients

Contraindications: Patients with a history of hypersensitivity to local anesthetics of the amide type, Patients with Stokes-Adams syndrome, Wolff-Parkinson- White syndrome, or with severe degrees of sinoatrial, atrioventricular, or intraventricular block.

Precautions: Do not rub or wipe the eye until the feeling in the eye returns. This may cause injury or damage to the eye.

Pregnancy: Avoid in early pregnancy

Breastfeeding: Not known to be harmful

Adverse effects: Blurred vision, sensitivity to light, throbbing pain, severe stinging, redness

Lignocaine +Epinephrine (Adrenaline)

ATC code: N01BB52

Eye drops, Lignocaine 2% + Adrenaline (1:100,000 or 1:200,000 as HCL), LOU 5

Indications and dose

Adult

A local anaesthetic for ophthalmic installation. Used to numb the eye before surgery, certain tests, or procedures. For most procedures, two drops once, however some procedures may require several applications.

Paediatric

Child >12 years

Contraindications: patients with a history of hypersensitivity to local anesthetics of the amide type, in patients with Stokes-Adams syndrome, Wolff-Parkinson- White syndrome, or with severe degrees of sinoatrial, atrioventricular, or intraventricular block.

Precautions: Do not rub or wipe the eye until the feeling in the eye returns. This may cause injury or damage to the eye.

Adverse effects: Blurred vision, sensitivity to light, throbbing pain, severe stinging, redness

Proparacaine

ATC code: S01HA04

Eye drop, 0.5% (as HCL), 5ml, LOU 4

Indications and dose

Adult

A local anaesthetic for ophthalmic installation. Used for the removal of corneal foreign bodies and also for procedures such as tonometry, gonioscopy, or similar eye tests requiring topical anesthesia of the conjunctiva and cornea, ocular for topical ophthalmic use: 1 or 2 drops prior to having surgery or procedure and 1 drop every 5 or 10 minutes for 5 to 7 doses for cataract extraction.

Paediatric

Child >12 years: same dose as adults

Contraindications: Contraindicated in patients with known hypersensitivity to any of the ingredients of this preparation.

Precautions: For topical ophthalmic use only. Prolonged use may produce permanent corneal opacification with accompanying loss of vision.

Pregnancy: Should be administered to a pregnant woman only if clearly needed.

Breastfeeding: Used with caution

Adverse effects: Blurred vision, sensitivity to light, throbbing pain, severe stinging, redness

Tetracaine

ATC code: S01HA03

Solution (eye drops), 0.5% (HCl), LOU 4

Indications and dose

Adult

Short-acting local anaesthesia of cornea and conjunctiva, by ocular instillation: 1 drop

Paediatric

Local anaesthesia, eye

Neonate, infant, or **child:** 1 drop repeated in 5 minutes if necessary to a maximum of 1 drop every 5 minutes for five doses

Contraindications: Hypersensitivity to ester-type local anaesthetics, eye inflammation or infection.

Precautions: Avoid prolonged use (cause of severe keratitis, permanent corneal opacification, scarring, delayed corneal healing), protect eye from dust and bacterial contamination until sensation fully restored, corneal scrapings: use preservative-free drops (preservative may affect microbiological culture).

Adverse effects: Common: Burning, stinging on initial instillation, redness, punctate epithelial damage of cornea (do not use long term because of epithelial toxicity, i.e. acute corneal ulceration).

Rare: Allergy.

Interaction with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

- Anaesthetic effect occurs within 3 minutes and lasts for 15 minutes or more. Close eyes after instillation and dab away tears without rubbing eyes. These eye drops may sting at first. Never prescribe for home use.
- Topical anaesthetics increase corneal permeability and intraocular bioavailability of other topical drugs, they also reduce the initial stinging of other topical drugs and should be instilled first. Single-use drops are useful if infection is suspected, otherwise avoid contaminating the tip of the solution bottle. WHO age/weight restriction: not in preterm neonates.
- Also referred to as amethocaine.

22.4. Miotics & Anti-Glaucoma Medicines

Acetazolamide

ATC code: S01EC01

Tablet, 250 mg, LOU 4

Indications and dose

Adult

Adjunct in treatment of chronic open-angle glaucoma, secondary glaucoma, part of preoperative treatment of acute angle-closure glaucoma, oral: 250mg to 1 g daily in divided doses

Paediatric

Adjunct in treatment of chronic open-angle glaucoma, secondary glaucoma, part of preoperative treatment of acute angle-closure glaucoma, oral

Infant and child below 12 years: 8 to 12 mg/kg daily in divided doses

Child above 12 years: 15 to 30 mg/kg daily in divided doses

Contraindications: hypersensitivity to sulfonamides, chronic angle-closure glaucoma (may mask deterioration), hypokalaemia, hyponatraemia, hyperchloraemic acidosis, renal impairment, severe hepatic impairment.

Precautions: the elderly, pregnancy and breastfeeding, diabetes mellitus, pulmonary obstruction, monitor blood count and electrolytes if used for long periods,

Adverse effects: nausea, vomiting, diarrhoea, taste disturbances, loss of appetite, paraesthesia, flushing, headache, dizziness, fatigue, irritability, depression, thirst, polyuria, reduced libido, metabolic acidosis and electrolyte disturbances on long-term therapy, occasionally drowsiness, confusion, hearing disturbances, urticaria, melaena, glycosuria, haematuria, abnormal liver function, renal calculi, blood disorders (including agranulocytosis and thrombocytopenia), and rash (including SJS and toxic epidermal necrolysis), transient myopia reported.

Interaction with other medicines: Methenamine, valproate, aspirin, zonisamide, lithium, methotrexate

Note:

- May impair ability to perform skilled tasks, for example operating machinery or driving.

Bimatoprost

ATC Code: S01EE03

Eye Drops, 0.01%, 0.03%, LOU 4

Indications and dose

Adult

Reduction of raised intra-ocular pressure in open-angle glaucoma and Ocular hypertension, ocular use: Apply once daily in the affected eye, preferably in the evening.

Paediatric

Safety and efficacy in children below 18 years has not yet been established.

Contraindications: Hypersensitivity to the active substance or to any of the excipients

Precautions: Angle-closure glaucoma, asthma, chronic obstructive pulmonary disease, compromised respiratory function, congenital glaucoma (no experience of use), contact lens wearers, patients with history of significant ocular viral infections (e.g. herpes simple), inflammatory ocular conditions (no experience of use), narrow-angle glaucoma (no experience of use), neovascular glaucoma (no experience of use), predisposition to bradycardia, predisposition to hypotension, pseudophakia with torn posterior lens capsule or anterior chamber lenses, patients with known risk factors for cystoid macular oedema

Hepatic impairment: Use with caution

Renal impairment: Use with caution

Pregnancy: Use only if potential benefit outweighs risk

Breastfeeding: Use only if potential benefit outweighs risk

Adverse effects: Dry eye, eye discolouration, eye discomfort, eye disorders, eye inflammation, headache, hypertension, hypertrichosis

Bimatoprost + Timolol

ATC Code: S01ED51

Solution (eye-drops), Bimatoprost 0.03% and Timolol 0.5%, LOU4

See individual monographs for bimatoprost and timolol

Brimonidine + Timolol

ATC Code: S01ED51

Solution (eye-drops), Brimonidine 0.2% and Timolol 0.5%, LOU5

Indication and Dose

Adult

Reduction of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers, By Instillation: One drop in the affected eye (s) twice daily.

Paediatric

less than 2 years of age (Neonates and infants): Contraindicated

2 to 17 years of age: Safety and effectiveness have not been established.

Contraindications

Neonates and infants, Brimonidine is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenergic transmission

Precautions

Children of 2 years of age and above,

Adverse Effects

Conjunctival hyperaemia, burning sensation, stinging sensation in the eye, allergic conjunctivitis, corneal erosion, superficial punctate keratitis, eye pruritus, conjunctival folliculosis, visual disturbance, blepharitis, epiphora, eye dryness, eye discharge, eye pain, eye irritation, foreign body sensation, visual acuity worsened, conjunctival oedema, follicular conjunctivitis, allergic blepharitis, conjunctivitis, vitreous floater, asthenopia, photophobia, papillary hypertrophy, eyelid pain, conjunctival blanching, corneal oedema, corneal infiltrates, and vitreous detachment

Dorzolamide

ATC code: S01EC03

Eye drops, 2% (as HCl), LOU 4

Indications and dose

Adult

Topical treatment of ocular hypertension and open angle glaucoma

Monotherapy: Instill 1 drop 3 times daily

Adjunctive therapy with a topical beta-blocker: Instill 1 drop twice daily

Paediatric: Follow adult dosing

Contraindications: hypersensitivity to dorzolamide or any product component

Precautions: the elderly, pregnancy and breastfeeding, diabetes mellitus, pulmonary obstruction, monitor blood count and electrolytes if used for long periods

Adverse effects: hypersensitivity reaction, metabolic acidosis, thrombocytopenia, angioedema, SJS, Toxic epidermal necrolysis, aplastic anaemia, local effects include bitter taste, burning, stinging or itching of the eye, blurred vision, tearing, conjunctivitis, eyelid inflammation.

Interaction with other medicines:

Memantine

Notes:

- Remove contact lenses prior to instillation. Lenses may be reinserted 15 minutes after instillation.
- Allow at least 5 minutes between instillation of multiple ophthalmic products.

Latanoprost

ATC code: S01EE01

Solution (eye-drops), 0.005%, LOU 4

Indications and dose

Adult

Reduction of elevated intraocular pressure in glaucoma and ocular hypertension in patients intolerant or unresponsive to other agents: Instill 1 drop once daily in the evening

Paediatric: Safety and efficacy is not established

Contraindications: Hypersensitivity to latanoprost or any component of the formulation

Precautions: Hepatic impairment, renal impairment

Adverse effects: brown pigmentation particularly in those with mixed-color irides, blepharitis, ocular

irritation and pain, conjunctival hyperaemia, transient punctuate epithelial erosion, skin rash, dry eyes, headache, and photophobia, they may also cause, darkening, thickening and lengthening of eye lashes.

Interaction with other medicines

Bimatoprost, tafluprost, thimerosal, travoprost, unoprostone, pilocarpine

Notes:

» Remove contact lenses prior to instillation. Lenses may be reinserted 15 minutes after instillation. Allow at least 5 minutes between instillation of multiple ophthalmic products.

Pilocarpine

ATC code: S01EB01

Solution (eye-drops), 1%, 2%, 4% (as HCl or nitrate), LOU 5

Injection (Ophthalmic solution – preservative free), 0.5%w/v (as nitrate), LOU5

Chronic open-angle glaucoma, ocular hypertension, emergency treatment of acute angle-closure glaucoma, to antagonize effects of mydriasis and cycloplegia following surgery or ophthalmoscopic examination

Indications and dose

Adult

Chronic open-angle glaucoma or ocular hypertension intraocular pressure, by ocular instillation: 1 drop up to 4 times daily every 6 hours; concentration of eye drops and frequency of administration should be adjusted as necessary to control intraocular pressure

Acute angle-closure glaucoma (before surgery), by ocular instillation: 1 drop (2% solution) every 10 minutes for 30–60 minutes, then 1 drop every 1–3 hours until intraocular pressure subsides

Postoperative elevated intraocular pressure by ocular instillation, 1%, 2%, or 4% solution: 1 to 2 drops to affected eye(s) 15 to 60 minutes before surgery

Miosis induction by ocular instillation, 1%, 2%, or 4% solution: 1 to 2 drops to affected eye(s)

Miosis induction, intracameral injection: Specialist Use

Paediatric: Follow adult dosing

Contraindications: acute iritis, acute uveitis, anterior uveitis, some forms of secondary glaucoma, acute inflammation of anterior segment, use not advisable after angle-closure surgery (risk of posterior synechiae). Hypersensitivity to any component of the formulation; where constriction is undesirable.

Precautions: retinal disease, conjunctival or corneal damage, monitor intraocular pressure in chronic open-angle glaucoma and in long-term treatment, cardiac disease, hypertension, asthma, peptic ulceration, urinary tract obstruction, Parkinson disease, withdraw treatment if symptoms of systemic toxicity develop.

Adverse effects: eye pain, blurred vision, ciliary spasm, lacrimation, myopia, browache, conjunctival vascular congestion, superficial keratitis, vitreous haemorrhage, and increased pupillary block reported, lens opacities (following prolonged use), rarely systemic effects including hypertension, tachycardia, bronchial spasm, pulmonary oedema, salivation, sweating, nausea, vomiting, and diarrhoea.

Interaction with other medicines:

Tegafur, latanoprost

Note:

» Causes difficulty with dark adaptation, may cause accommodation spasm.

» Advice patients not to carry out skilled tasks, for example, operating machinery or driving until vision is clear.

» If 2 drops are to be administered, they should be instilled 5 minutes apart

Timolol

ATC code: S01ED51

Eye drops 0.5% (as hyd. maleate), LOU 4

Indications and dose

Adult

Ocular hypertension, chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas, *by ocular instillation:* 1 drop twice daily

Paediatric

Ocular hypertension, open-angle glaucoma

Child 2 years and above: Instill 1 drop in affected eye(s) once daily

Contraindications: uncontrolled heart failure, bradycardia, heart block, asthma or history of obstructive airways disease, hypersensitivity to any component of this product.

Precautions: elderly (risk of keratitis), in angle-closure glaucoma, use with a miotic and not alone.

Adverse effects: stinging, burning, pain, itching, erythema, transient dryness, allergic blepharitis, transient conjunctivitis, keratitis, decreased corneal sensitivity, diplopia, ptosis, systemic effects, particularly on the pulmonary, cardiovascular and CNSs, may follow absorption.

Notes:

» Advice patient to report symptoms of eye infection. Drug may cause transient blurred vision, warn patient to avoid driving or other activities requiring clear vision until drug effects clear

22.5. Mydriatics

Atropine

ATC code: S01FA01

Solution (eye drops), 0.1%, 0.5%, 1% (sulphate) LOU 4

Indications and dose

Adult

Cycloplegic refraction, by ocular instillation: 1 drop (1% solution) twice daily for 1–2 days before procedure or a single application of 1 drop (1% solution) 1 hour before procedure

Iritis, uveitis, by ocular instillation: 1 drop (0.5% or 1% solution) up to 4 times daily

Paediatric

Cycloplegic refraction, eye

Infant 3 months–1 year: 1 drop (0.1%) twice daily for 1–3 days before procedure with a further dose given 1 hour before procedure

Child 1–5 years: 1 drop (0.1–0.5%) twice daily for 1–3 days before procedure with a further dose given 1 hour before procedure

Child over 5 years: 1 drop (0.5–1%) twice daily for 1–3 days before procedure with a further dose given 1 hour before procedure

Iritis, uveitis, eye

Infant over 3 months: 1 drop (0.5 or 1%) up to three times daily

Contraindications: Closed angle glaucoma.

Precautions: May precipitate acute attack of closed angle glaucoma, significant head injury (use only short-acting agents with care, always make a note that pupils were dilated intentionally). Use with extreme caution, if at all, in children with spastic paralysis or brain damage (increased susceptibility to systemic reactions). 1 drop of 0.5% atropine can cause systemic effects in infants. In young children, long-term cycloplegia may induce amblyopia.

Adverse effects: Common Intolerance to bright light (glare), stinging on instillation, blurred vision (especially near vision), transient intraocular pressure elevation.

Conjunctivitis, contact allergic blepharitis, persistent ocular irritation (mucus discharge, severe watering discharge, superficial punctate keratopathy and characteristically no itch), punctal stenosis with prolonged use (years), insomnia.

Rare Systemic toxicity (may be more frequent in children), e.g., dryness of skin and mouth, fever, facial flushing, tachycardia, irritability, disorientation, ataxia, visual hallucinations, incoherent speech, delirium, psychosis, seizures, hyperactivity.

Interaction with other medicines:

There are no known interactions where it is recommended to avoid concomitant use.

Notes:

Avoid contaminating the tip of the solution bottle.

Apply finger pressure to the lacrimal sac during and for 1–2 minutes after instillation to decrease risk of absorption and systemic effects.

Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery. Blurred vision may persist for up to 14 days after administration.

WHO age/weight restriction: > 3 months.

Cyclopentolate

ATC code: S01FA04

Eye drops, 0.5%, 1%, 2%, LOU 4

Indications and dosage

Adult

Mydriasis/cycloplegia: Instil 1-2 drops of 0.5%, 1% or 2% solution in the eye which may be repeated in five to ten minutes if necessary. In adults, use 2% in highly pigmented iris. Wait 5 minutes between drops.

Paediatrics

Cycloplegia

To the eye

Child 3 months–11 years: Instil 1 drop, 30–60 minutes before examination, using 1% eye drops

Child 12–17 years: Instil 1 drop, 30–60 minutes before examination, using 0.5% eye drops

Uveitis

To the eye

Child 3 months–17 years: Instil 1 drop 2–4 times a day, using 0.5% eye drops (1% for deeply pigmented eyes)

Contraindications: Hypersensitivity, untreated narrow angle glaucoma, increased intraocular pressure, untreated narrow angles.

Precautions: Down syndrome – predisposed to angle-closure glaucoma. Elderly - predisposed to increased intraocular pressure.

Pregnancy: Use with caution if benefit outweighs risk.

Breastfeeding: Use with caution.

Adverse effects: Blurred vision, burning sensation in the eye, light intolerance, tachycardia, conjunctivitis, raised intraocular pressure, hyperactive response in Down's syndrome, drowsiness, eye oedema

Interactions with other medicines: Clozapine, amitryptilline, atropine

Notes:

- Transient elevation in intraocular pressure may occur.
- The 2% solution may result in psychotic reactions and behavioural disturbances in children 30-45mins following instillation.
- Physostigmine can be given in severe systemic ADRs.

Tropicamide + phenylephrine

ATC code: S01FA06

Eye drops,0.8% + 5% w/v, LOU 4

Indications

Adult

Inflammatory conditions of the uveal tract: 1–2 drops 2 to 4 times daily or as required

Diagnostic (Retinal photography, refractive errors, fundus examination/photography, slit lamp examination), Pre-operative (Dilate pupil to visualize structures

behind the iris before surgical procedures, such as cataract extraction, vitrectomy, and retinal detachment surgery): 1–2 drops in the eye(s) 15–30 minutes prior to the procedure

Paediatric: Follow adult dosing

Contraindications: Hypersensitivity to the medicine and any components of the formulation, narrow angles or narrow angles glaucoma.

Precautions: Pregnancy, breastfeeding, children

Adverse effects: May cause elevated Intra ocular pressure, stinging on application, dryness of the mouth, blurred vision, tachycardia, photophobia with or without corneal staining, headache, parasympathetic stimulation and allergic reactions.

Interaction with other medicines: MAO inhibitors, tricyclic antidepressants

Note:

» Causes photophobia, advice patient to wear sunglasses outside and avoid bright lights until drug effects subside.

22.6. Anti-Vascular Endothelial Growth Factor Preparations

Aflibercept

ATC code: S01LA05

Injection, 0.05ml (2mg vial), LOU 6

Indications and dose

Adult

Treatment of macular edema following retinal vein occlusion, Diabetic Macular edema and Diabetic retnopathy, Intravitreal, 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks for the first 5 doses, followed by 2 mg every 8 weeks. Some patients may need every 4 weeks dosing after the first 20 weeks.

Treatment of macular degeneration, Intravitreal, 2 mg (0.05 mL) by intravitreal injection every 4 weeks for first 3 doses, followed by 2 mg every 8 weeks. Some patients may need to be dosed as frequently as 2 mg every 4 weeks.

Pediatric:

Treatment of retinopathy of prematurity, Intravitreal, 0.4 mg (0.01 mL) by intravitreal injection. Initiate treatment with a single injection per eligible eye; may be administered bilaterally on the same day. Injections may be repeated in each eye. Treatment interval between doses injected into the same eye should be at least 10 days.

Contraindications: Hypersensitivity reactions, Ocular or periocular infection, active intraocular inflammation.

Precautions: Acute increases in intraocular pressure (IOP) observed within 60 minutes of intravitreal injection; sustained increases also reported after repeat dosing; monitor and manage IOP and perfusion of optic nerve head. Endophthalmitis and retinal detachments reported with intravitreal injections; instruct patients and/or caregivers to report any signs and/or symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Risk of arterial thromboembolic events (e.g., nonfatal stroke, nonfatal myocardial infarction, or vascular death) following intravitreal use of VEGF inhibitors.

Pregnancy: May pose a risk to fetal development given anti-VEGF mechanism.

Breastfeeding: Not recommended during breastfeeding, potential for harm to infant growth and development exists.

Adverse effects: Eye pain, Cataracts, Conjunctival haemorrhage, Increased IOP, Vitreous detachment, Vitreous floaters, Corneal epithelium defect, Retinal pigment epithelium detachment, Ocular hyperemia, foreign body sensation in eyes, Lacrimation increased, Blurred vision, Intraocular inflammation, Injection site pain, Retinal pigment epithelium tear, Injection site haemorrhage, Eyelid edema, Corneal edema.

Notes:

» Treatment interval between doses injected into the same eye should be at least 10 days. Hypersensitivity reactions may present as severe intraocular inflammation. Females of reproductive potential should use effective contraception prior to initial dose, during treatment, and for at least 3 months after last intravitreal injection.

Bevacizumab

ATC code: L01XC07

Injection, 25 mg/mL (4-mL vial), LOU 6

Indications and dose

Adult

Age related macular degenretaion, cystoid macular oedema and retinal vein occlusion or other macular diseases, diabetic retinopathy, diabetic macular oedema, intravitreal: 1.25mg in the affected eye before vitrectomy

Paediatric

Retinopathy of prematurity, intravitreal: 0.375mg to 0.625mg in the affected eye

Contraindications: hypersensitivity to Bevacizumab, murine products, or any component of the formulation, pregnancy and breastfeeding.

Precautions: Heart disease, stroke, or bleeding disorder

Adverse effects: cataract formation, glaucoma, bleeding, hypotony, damage to the retina or cornea, endophthalmitis

Note:

Not to be mixed with dextrose-containing solutions

Ranibizumab

ATC code: S01LA04

Injection, 10mg/ml (0.5mg vial), 6mg/ml (0.3mg vial), LOU 5

Indications and dose

Adult

Ovascular (Wet) Age-Related Macular Degeneration (AMD): 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Macular Edema Following Retinal Vein Occlusion (RVO): 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Diabetic Macular Edema (DME): 0.3 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Myopic Choroidal Neovascularization (mCNV): 0.5 mg (0.05 mL of 10 mg/mL solution) intravitreal injection once a month initially, for up to 3 months. May retreat if needed, based on assessment of mean baseline change in visual acuity.

Diabetic Retinopathy: 0.3 mg (0.05 mL of 6 mg/mL solution) intravitreally once a Month (approximately 28 days)

Paediatric:

Safety and efficacy not established

Contraindications: Ocular or periocular infections. Hypersensitivity to the active ingredient or the products excipients.

Renal impairment: No dosage adjustment necessary

Pregnancy: No adequate and well-controlled studies in pregnant women

Breastfeeding: No data available on presence of ranibizumab in human milk

Adverse effects: Conjunctival hemorrhage, eye pain, vitreous floaters, endophthalmitis and retinal detachments, increases in intraocular pressure thromboembolic events, fatal events in diabetes macular edema patients.

Interactions with other medicines: Verteporfin

Note:

Potential for adverse thromboembolic events (e.g., non-fatal stroke, non-fatal myocardial infarction, vascular death), temporary visual disturbances may occur.

22.7. Anti-Allergy Medicines For the Eye

Azelastine

ATC code: S01GX07

Eye drops 0.05%, LOU 2

Indications and dose

Adult

Seasonal allergic conjunctivitis, perennial conjunctivitis, eye: 1 drop instilled twice daily in the affected eye(s), increased if necessary to 4 times a day; maximum duration of treatment is 6 weeks

Paediatric

Child below 4 years: Safety and efficacy is not established

Seasonal allergic conjunctivitis, perennial conjunctivitis, eye:

Child 4–17 years: 1 drop instilled twice daily in the affected eye(s), increased if necessary to 4 times a day

Seasonal allergic conjunctivitis, perennial conjunctivitis, eye:

Child 12–17 years: 1 drop instilled twice daily in the affected eye(s), increased if necessary to 4 times a day maximum duration of treatment 6 weeks

Contraindications: hypersensitivity to azelastine or any component of the product

Precautions: pregnancy and breastfeeding

Adverse effects: Common or very common: Eye irritation, taste bitter (if applied incorrectly)

Interaction with other medicines

Amifampridine, bupropion, donepezil, pitolisant, cimetidine

Notes:

» Advise patient to remove contact lens if eyes are red. If eyes are not red, contacts may be inserted 10 minutes after instillation

Olopatadine

ATC code: S01GX09

Ophthalmic solution 0.1%, 0.2%, LOU 5

Indications and dose

Adult

Allergic Conjunctivitis

0.1% solution: 1 drop in affected eye(s) at an interval of 6-8 hrs

0.2% solution: 1 drop in affected eye(s) once daily

Treatment may be maintained for up to four months, if considered necessary.

No dosage adjustment in elderly patients is necessary.

Paediatric

Infant or **child <2 years:** Safety and efficacy not established

Older than 2 years: *Same as for adult*

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Precautions: contains benzalkonium chloride which may cause eye irritation. Benzalkonium chloride has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent or prolonged use in dry eye patients, or in conditions where the cornea is compromised. Benzalkonium is known to discolour soft contact lenses. Avoid contact with soft contact

lenses. Patients should be instructed to remove contact lenses prior to administration of the eye drop and wait at least 15 minutes after instillation before re-inserting contact lenses.

Hepatic or renal impairment: no dosage adjustment is expected to be necessary in hepatic or renal impairment.

Pregnancy and breast feeding: not recommended during pregnancy and in women of childbearing potential not using contraception. Should not be used during breast-feeding.

Adverse effects: Asthenia, dry eye, eye discomfort, headache, nasal dryness, taste altered, dizziness, eye disorders, eye inflammation, increased risk of infection, numbness, skin reactions, vision disorders, drowsiness, dyspnea, malaise, nausea, vomiting.

Interactions: No interaction studies with other medicinal products have been performed.

Sodium cromoglicate

ATC code: S01GX01

Eye drops 2%, LOU 5

Indications and dose

Adult

Allergic conjunctivitis, allergic kerato conjunctivitis, topical ophthalmic: 4 times daily (2%), one or two drops into each eye up to four times a day or as indicated by the doctor.

Paediatric: Follow adult dosing

Contraindication: Hypersensitivity to sodium cromoglicate

Precautions: Hypersensitivity, do not exceed frequency of administration

Adverse effects: Transient burning

Interaction with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

» Advise patient not to wear contact lenses during therapy with the drug

22.8. Other Medicines For the Eye

Hypertonic saline

ATC code: S01XA03

Eye drops 3%, LOU 5

Indications and dose

Adult

Short term relief of corneal edema, can be used as comfort drops by contact lens users to facilitate lens removal, tear deficiency, bullous keratopathy: Apply as required

Paediatric: Follow adult dosing

Contraindication: Hypersensitivity

Precautions: Hypersensitivity

Adverse effects: Eye discomfort, burning, redness, temporary blurred vision

Interaction with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

» Remove contact lens, do not touch the tip of the vial

Methyl cellulose

ATC code: S01XA20

Eye drops 0.3–1%, LOU 4

Indications and dose

Adult

Relieve dry and irritated eyes: Instill as often as needed

Paediatric: Follow adult dosing

Polyacrylic acid

ATC code: S01XA20

0.2% w/w gel tears, LOU 4

Indications and dose

Adult

Dry eyes including keratoconjunctivitis sicca, unstable tear film: One drop to be instilled into the conjunctival fold of each affected eye 3 - 4 times daily or as required, depending on the degree of discomfort.

Paediatric: Same as adult

Contraindications: Hypersensitivity to the active substance or to any of the excipients

Precautions: Blurred vision can occur if too much gel is instilled at one time, or if the gel is used too frequently. This effect can last for up to an hour. Recovery can be aided by blinking vigorously for a few seconds. If this fails, the lower eyelid should be manipulated until the gel returns to the lower fornix and normal vision is restored.

Pregnancy & Breast Feeding: Safety for use in pregnancy and lactation has not been established, therefore, Gel tears should not be used in these circumstances.

Adverse effects: Corneal irritation due to benzalkonium chloride could possibly occur with prolonged use. Transient blurring of vision may occur on instillation. If affected, the patient should be advised not to drive or operate hazardous machinery until normal vision is restored.

Interactions with other medicines: No significant interactions have been reported.

Riboflavin

ATC code: S01XA26

Topical ophthalmic solution in 2-3mL glass syringe, 0.1% without Dextran, 0.1% with Dextran, LOU 5

Indications and dose

Adult

Progressive Keratoconus; Corneal Ectasia, Topical: Instill 1 drop of Viscous form topically on the eye every 2 minutes for 30 minutes; examine the eye under the slit lamp for the presence of a yellow flare; If the yellow flare is not detected, instill 1 drop of Viscous formulation every 2 minutes for an additional 2-3 drops and recheck for the presence of a yellow flare; this process can be repeated as necessary.

Once the yellow flare is observed, perform ultrasound pachymetry.

If corneal thickness is <400 micrometers, instill 2 drops of non-viscous formulation every 5-10 seconds until the corneal thickness increases to at least 400 micrometers. During irradiation, continue topical instillation of Viscous formulation onto the eye every 2 minutes for the 30-minute irradiation period.

Paediatric

<14yrs: Safety and efficacy not established

14yrs and older: Same as adult

Contraindications: Hypersensitivity to drug or ingredient

Precautions: Ulcerative keratitis can occur; monitor for resolution of epithelial defects

Pregnancy: Weigh risk/benefit during pregnancy; no human or animal data available

Breastfeeding: Weigh risk/benefit while breastfeeding; no human data available to assess risk of infant harm or effects on milk production

Adverse effects (*indicates serious): ulcerative keratitis*, Corneal opacity, cunctate keratitis, corneal striae, corneal epithelium defect, eye pain, vision blurred, foreign body sensation in eyes ,ocular hyperemia, photophobia, visual acuity reduced, headache, dry eye, eyelid edema, increased lacrimation.

Interactions with other medicines: No significant interactions known or found for this drug.

Notes: Viscous form contains riboflavin in dextran solution; reserve non-viscous form for corneal thickening.

Sodium Hyaluronate

ATC code: S01KA01

Eye drops; 1% preservative free, LOU 4

Indications and dose

Adult

Dry eyes: instill 1 drop 2-3times daily

Paediatric: Same as for adult

Adverse effects: minor burning, stinging or irritation may occur temporarily, hypersensitivity reactions.

Trypan Blue

ATC code: S01KX02

Intracameral solution, 0.06%, 0.5 mL in a sterile single-use Luer, 2.25 mL glass syringe Lok, LOU 5

Indications and dose

Ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

Adult

After opening the eye, an air bubble is injected into the anterior chamber of the eye in order to minimize dilution of trypan blue by the aqueous. Carefully apply onto the anterior lens capsule using a blunt cannula. Sufficient staining is achieved as soon as the dye has contacted the capsule. The anterior chamber is then irrigated with balanced salt solution to remove all excess dye.

Paediatric: Same as for adult

Contraindications: contraindicated when a non-hydrated, hydrophilic acrylic intraocular lens is planned to be inserted into the eye.

Precautions: It is recommended that after injection all excess trypan blue be immediately removed from the eye by thorough irrigation of the anterior chamber.

Pregnancy: Teratogenic Effects, give to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding: It is not known whether this drug is excreted in human milk.

Adverse effects: temporary blue coloration of the eye, staining of implanted lenses.

23. Medicines For Reproductive Health & Perinatal Care

23.1. Contraceptives

23.1.1. Oral Hormonal Contraceptives

Ethinylestradiol + Levonorgestrel

ATC code: G03AA07, G03AB03

Tablet, 30 micrograms + 150 micrograms, LOU 2

Indications and dose

Adult

Contraception, oral, female: 1 tablet daily for 21 days, subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs)

Contraception, oral, everyday preparations, female: 1 active tablet daily started on day 1 of the cycle, subsequent courses repeated without interval (withdrawal bleeding occurs when inactive tablets are being taken)

Adolescent, female:

Contraception, Refer to adult dose

Contraindications: use within 3 weeks of birth, breastfeeding (until weaning or for the first 6 months after birth), personal history of two or more risk factors for venous thromboembolism and arterial disease, heart disease associated with pulmonary hypertension or risk of embolism, migraine with typical focal aura, severe migraine without aura but regularly lasting over 72 hours duration despite treatment or migraine treated with ergot derivatives, history of sub-acute bacterial endocarditis, ischaemic cerebrovascular disease, liver disease including disorders of hepatic secretion such as Dubin-Johnson and Rotor syndromes, infectious hepatitis (unless liver function is restored to normal), porphyria, SLE, liver adenoma, history of haemolytic uraemic syndrome, gallstones, estrogen-dependent neoplasms, neoplasms of breast or genital tract, undiagnosed vaginal bleeding, history during pregnancy of pruritus, chorea, deteriorating otosclerosis, cholestatic jaundice, or pemphigoid gestationis, after evacuation of hydatidiform mole unless urine and plasma gonadotrophin values are restored to normal).

Precautions: risk factors for venous thromboembolism and arterial disease, migraine without focal aura or controlled with 5HT1 agonist, hyperprolactinaemia, some types of hyperlipidaemia, gallbladder disease, history of severe depression especially if induced by hormonal contraception, long-term immobilization, sickle-cell disease, inflammatory bowel disease including Crohn disease

Hepatic Impairment: Contraindicated in patients with hepatic impairment.

Renal Impairment: Dose adjustment not necessary. Use with caution and monitor blood pressure.

Pregnancy: Use is contraindicated in pregnancy

Breastfeeding: infant risk cannot be ruled out.

Adverse effects: nausea, vomiting, headache, breast tenderness, increase in body weight, thrombosis, changes in libido, depression, chorea, skin reactions, chloasma, hypertension, impairment of liver function, "spotting" in early cycles, absence of withdrawal bleeding, irritation of contact lenses, rarely photosensitivity reactions and hepatic tumours, increased risk of breast cancer.

Interaction with other medicines (*indicates serious)

*Ritonavir, *tranexamic acid, *penicillins, aprepitant, artemether, betamethasone, bupropion, anti-epileptics, cephalosporins, cloxacillin, cyclosporine, darunavir, dexamethasone, doxycycline, isotretinoin, ocreotide, piperaquine, rifampicin, rifabutin, St. John's Wort, sugammadex, theophylline, diazepam, etoricoxib, ginseng, levothyroxine, prednisolone, selegiline, warfarin

Notes:

- Each tablet ("pill") should be taken at approximately the same time each day, if delayed by longer than 24 hours, contraceptive protection may be lost.
- Missed pill. The critical time for loss of contraception protection is when a pill is omitted either at the *beginning* or at the *end* of a cycle (this lengthens the pill free interval). If a woman forgets to take a pill, she should take it as soon as she remembers, and take the next one at the normal time. If the delay with any pill is 24 hours or longer (but especially with the first one in the packet), the pill may not work. She should still continue taking the pill normally but be aware that she will not be protected for the next 7 days and must therefore either not have sex or use another method of contraception, such as a condom. If these 7 days run beyond the end of the packet, the next packet should be started at once, omitting the pill-free interval (or, in the case of everyday pills, omitting the 7 inactive tablets). Emergency contraception is recommended if more than 2 combined oral contraceptive tablets are missed from the first 7 tablets in a packet.
- Diarrhoea and vomiting. Vomiting within 2 hours of taking an oral contraceptive or very severe diarrhoea can interfere with the absorption of the pill. Additional precautions should be used during, and for 7 days after recovery. If vomiting and diarrhoea occur during the last 7 pills, the next pill-free period should be omitted (or in the case of everyday tablets, the inactive ones should be omitted).
- Migraine. Patients should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour).
- Travel. Women taking oral contraceptives may

be at increased risk of deep-vein thrombosis during travel involving long periods of immobility (over 5 hours). The risk may be reduced by appropriate exercise during the journey, and possibly by wearing elastic hosiery.

Ethinylestradiol + Norethisterone

ATC code: G03AA05, G03AB04

Tablet, 35 micrograms + 1 mg, LOU 2

Indications and dose

Adult

Contraception, oral, female: 1 tablet daily for 21 days, subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs)

Contraception, oral, everyday preparations, female: 1 active tablet daily started on day 1 of the cycle; subsequent courses repeated without interval (withdrawal bleeding occurs when inactive tablets are being taken)

Adolescent, female:

Contraception, Refer to adult dose

Contraindications: use within 3 weeks of birth, breastfeeding (until weaning or for the first 6 months after birth), personal history of two or more risk factors for venous thromboembolism and arterial disease, heart disease associated with pulmonary hypertension or risk of embolism, migraine with typical focal aura, severe migraine without aura but regularly lasting over 72 hours duration despite treatment or migraine treated with ergot derivatives, history of sub-acute bacterial endocarditis, ischaemic cerebrovascular disease, liver disease including disorders of hepatic secretion such as Dubin-Johnson and Rotor syndromes, infectious hepatitis (unless liver function is restored to normal), porphyria, SLE, liver adenoma, history of haemolytic uraemic syndrome, gallstones, estrogen-dependent neoplasms, neoplasms of breast or genital tract, undiagnosed vaginal bleeding, history during pregnancy of pruritus, chorea, deteriorating otosclerosis, cholestatic jaundice, or pemphigoid gestationis, after evacuation of hydatidiform mole (unless urine and plasma gonadotrophin values are restored to normal).

Precautions: risk factors for venous thromboembolism and arterial disease, migraine without focal aura or controlled with 5HT1 agonist, hyperprolactinaemia, some types of hyperlipidaemia, gallbladder disease, history of severe depression especially if induced by hormonal contraception, long-term immobilization, sickle-cell disease, inflammatory bowel disease including Crohn disease.

Hepatic Impairment: Contraindicated in patients with hepatic impairment.

Renal Impairment: Dose adjustment not necessary. Use with caution and monitor blood pressure.

Pregnancy: Use is contraindicated in pregnancy

Breastfeeding: infant risk cannot be ruled out.

Adverse effects: nausea, vomiting, headache, breast tenderness, increase in body weight, thrombosis, changes in libido, depression, chorea, skin reactions, chloasma, hypertension, impairment of liver function, "spotting" in early cycles, absence of withdrawal bleeding, irritation of contact lenses, rarely photosensitivity reactions and hepatic tumours, increased risk of breast cancer

Interaction with other medicines (*indicates serious)

*Ritonavir, *tranexamic acid, *penicillins, aprepitant, artemether, betamethasone, bupropion, anti-epileptics, cephalosporins, cloxacillin, cyclosporine, darunavir, dexamethasone, doxycycline, isotretinoin, ocreotide, piperaquine, rifampicin, rifabutin, St. John's Wort, sugammadex, theophylline, diazepam, etoricoxib, ginseng, levothyroxine, prednisolone, selegiline, warfarin

Notes:

- Each tablet ("pill") should be taken at approximately the same time each day, if delayed by longer than 24 hours, contraceptive protection may be lost.
- Missed pill. The critical time for loss of contraception protection is when a pill is omitted either at the *beginning* or at the *end* of a cycle (as this lengthens the pill free interval). If a woman forgets to take a pill, she should take it as soon as she remembers, and take the next one at the normal time. If the delay with any pill is 24 hours or longer (but especially with the first one in the packet), the pill may not work. She should still continue taking the pill normally but be aware that she will not be protected for the next 7 days and must therefore either not have sex or use another method of contraception, such as a condom. If these 7 days run beyond the end of the packet, the next packet should be started at once, omitting the pill-free interval (or, in the case of everyday pills, omitting the 7 inactive tablets). Emergency contraception is recommended if more than 2 combined oral contraceptive tablets are missed from the first 7 tablets in a packet.
- Diarrhoea and vomiting. Vomiting within 2 hours of taking an oral contraceptive or very severe diarrhoea can interfere with the absorption of the pill. Additional precautions should be used during, and for 7 days after recovery. If vomiting and diarrhoea occur during the last 7 pills, the next pill-free period should be omitted (or in the case of ed tablets, the inactive ones should be omitted).
- Migraine. Patients should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour).
- Travel. Women taking oral contraceptives may be at increased risk of deep-vein thrombosis during travel involving long periods of immobility (over 5 hours). The risk may be reduced by appropriate exercise during the journey, and possibly by wearing elastic hosiery.

Levonorgestrel

ATC code: G03AA07

Tablet, 30 micrograms, LOU 2

Indications and dose

Adult

Contraception (particularly when estrogens are contraindicated), oral, female: 1 tablet (30 micrograms) daily, starting on day 1 of the cycle and then continuously

Adolescent, female:

Contraception, Refer to adult dose

Contraindications: severe arterial disease, liver tumours, history of breast cancer (may be used after 5 years if no evidence of current disease), thromboembolic disorders, porphyria,

Precautions: undiagnosed vaginal bleeding, cardiac disease, past ectopic pregnancy, active liver disease, recurrent cholestatic jaundice, migraine, diabetes mellitus, breastfeeding.

Hepatic Impairment: Contraindicated in patients with hepatic impairment.

Renal Impairment: Dose adjustment not necessary. Use with caution and monitor blood pressure.

Pregnancy: Use is contraindicated in pregnancy

Breastfeeding: infant risk cannot be ruled out.

Adverse effects: menstrual irregularities, nausea, vomiting, headache, dizziness, breast discomfort, depression, skin disorders, disturbances of appetite, weight increase, change in libido, breast

Interaction with other medicines (*indicates serious)

Ritonavir, tranexamic acid, *penicillins, aprepitant, artemether, betamethasone, anti-epileptics, cephalosporins, ceritinib, cloxacillin, cyclosporine, darunavir, dexamethasone, doxycycline, efavirenz, griseofulvin, isotretinoin, nevirapine, ocreotide, piperaquine, rifampicin, rifabutin, St. John's Wort, sugammadex, theophylline, diazepam, etoricoxib, licorice, prednisolone, selegiline, warfarin

Notes:

- Each tablet ("pill") should be taken at approximately the same time each day. If delayed for longer than 3 hours, contraceptive protection may be lost.
- Missed pill. If a pill is not taken on time, it should be taken as soon as possible, and the next one taken at the usual time. If administration is delayed by more than 3 hours, the woman should resume taking the pill at the usual time as soon as possible, furthermore, because contraceptive efficacy is reduced, an additional method of contraception (such as a condom) is required for 2 days. Emergency contraception may be considered if 1 or more progestogen-only contraceptive pills are missed or taken more than 3 hours late and intercourse has occurred before 2 further tablets have been taken correctly.
- Diarrhoea and vomiting. Vomiting within 2 hours of taking an oral contraceptive or very severe diarrhoea can interfere with the absorption of the pill. Additional precautions should be used during and for 2 days after recovery.
- Administration. Taking emergency contraception as soon as possible after unprotected intercourse increases its efficacy; however, it should not be administered if menstrual bleeding is already overdue.

For Emergency Contraception

Levonorgestrel

ATC code: G03AD01

Tablet, 750 micrograms (pack of 2), LOU 2

Indications and dose

Adult

Emergency (post-coital) contraception, oral, female: 1.5 mg as a single dose (taken within 120 hours [5 days] of unprotected intercourse) or 750 micrograms (taken within 72 hours of unprotected intercourse) followed by a second dose of 750 micrograms 12 hours later

Adolescent, female:

Contraception, Refer to adult dose

Contraindications: Porphyria.

Precautions: undiagnosed vaginal bleeding, cardiac disease, past ectopic pregnancy, active liver disease, recurrent cholestatic jaundice, migraine, diabetes mellitus, breastfeeding.

Hepatic Impairment: Contraindicated in patients with hepatic impairment.

Renal Impairment: Dose adjustment not necessary.

Pregnancy: Use is contraindicated in pregnancy

Breastfeeding: infant risk cannot be ruled out.

Adverse effects: menstrual irregularities nausea, vomiting, headache, dizziness, breast discomfort, depression, skin disorders, disturbances of appetite, weight increase, change in libido

Interaction with other medicines (*indicates serious)

*Ritonavir, *tranexamic acid, *penicillins, aprepitant, artemether, betamethasone, anti-epileptics, cephalosporins, ceritinib, cloxacillin, cyclosporine, darunavir, dexamethasone, doxycycline, efavirenz, griseofulvin, isotretinoin, nevirapine, ocreotide, piperaquine, rifampicin, rifabutin, St. John's Wort, sugammadex, theophylline, diazepam, etoricoxib, licorice, prednisolone, selegiline, warfarin

Note:

- Taking emergency contraception as soon as possible after unprotected intercourse increases its efficacy, however, it should not be administered if menstrual bleeding is already overdue.

23.1.2. Injectable Hormonal Contraceptives

Medroxyprogesterone Acetate

ATC code: G03AC06

Depot injection (IM) 150 mg/1 mL (prefilled syringe), LOU 2

Depot injection (SC) 104 mg/0.65 mL (prefilled syringe), LOU 2

Indications and dose

Adult

Contraception, female, by deep IM injection, 150 mg within the first 7 days of cycle or within the first 5 days after parturition (delay until 6 weeks after parturition if breastfeeding), repeated every 3 months.

Contraception, female, by SC injection: 104 mg every 3 months), Adult (female), as for short-term, repeated every 3 months.

Adolescent, female:

Contraception, Refer to adult dose

Contraindications: pregnancy, history of breast cancer (may be used after 5 years if no evidence of current disease), undiagnosed vaginal bleeding, history of pruritus during pregnancy, active liver disease, severe arterial disease, multiple risk factors for venous thromboembolism and arterial disease, porphyria.

Precautions: migraine, liver disease, thromboembolic or coronary vascular disease, diabetes mellitus, hypertension, renal disease, epilepsy, asthma

Hepatic impairment: Contraindicated in patients with hepatic impairment.

Renal Impairment: No dose adjustment necessary.

Pregnancy: Contraindicated in pregnancy.

Breastfeeding: Infant risk cannot be ruled out.

Adverse effects: menstrual irregularities, delayed return to fertility, reduction in bone mineral density, weight gain, weight loss, depression, rarely anaphylaxis, injection-site reactions, increased risk of breast cancer, acne, abdominal pain, headache, nervousness

Interaction with other medicines (*indicates serious)

*Ritonavir, *tranexamic acid (contraindicated), *griseofulin aprepitant, artemether, anti-epileptics, darunavir, dexamethasone, efavirenz, griseofulvin, isotretinoin, mycophenolic acid, nevirapine, prednisolone, rifampicin, rifabutin, St. John's Wort, sugammadex, theophylline

Notes:

- If the interval between injections is greater than 3 months and 14 days, exclude pregnancy before administering the next injection and advise patient to use additional contraceptive measures (for example, a condom) for 7 days after the injection.
- Patient advice. It is recommended that before treatment, women receive full counselling (backed by a manufacturer's approved leaflet if possible) about the likelihood of menstrual irregularities and the potential for a delay in return to full fertility with long-term use.

23.1.3. Intrauterine Devices (Iud)

Copper-Containing Device

ATC code: G02BA02

LOU 2

Indications and dose

Adult

Contraception, female: Inserted at any time between day 4 and day 12 after the start of menstrual bleeding; do not fit during heavy menstrual bleeding

Emergency contraception, female: Inserted up to 120 hours (5 days) after unprotected intercourse, at any time of the menstrual cycle; if intercourse has occurred more than 5 days previously, the device can still be inserted up to 5 days after the earliest likely calculated day of ovulation

Continuation of contraception: Replaced by the end of 10 years. When it is time to replace, a new device may be inserted immediately after the previous IUD is removed, if otherwise appropriate. Device should not be left in place for >10 years.

The device can be removed at the beginning of menstruation if no longer required.

Adolescent, female:

Contraception, Refer to adult dose

Contraindications: pregnancy, severe anaemia, use within 48 hours-4 weeks of birth, puerperal sepsis, post-septic abortion, cervical or endometrial cancer, pelvic inflammatory disease, recent sexually transmitted disease (if not fully investigated and treated), pelvic TB, unexplained uterine bleeding, active trophoblastic disease, distorted or small uterine cavity, copper allergy, Wilson disease, medical diathermy.

Precautions: anaemia, heavy menstrual bleeding, endometriosis, severe primary dysmenorrhoea, history of pelvic inflammatory disease, ovarian cancer, fertility problems, nulliparity and young age, severely scarred uterus or severe cervical stenosis, valvular heart disease or history of endocarditis (antibacterial cover recommended at insertion), HIV infection or immunosuppressive therapy (increased risk of infection, avoid if marked immunosuppression), increased risk of expulsion if inserted before uterine involution, gynaecological examination before insertion and 4–6 weeks afterwards (counsel women to see doctor promptly if significant symptoms such as pain occur) anticoagulant therapy, remove if pregnancy occurs (consider possibility of ectopic pregnancy).

Hepatic impairment: Dose adjustment not necessary

Renal impairment: Dose adjustment not necessary.

Pregnancy: Contraindicated in pregnancy

Breastfeeding: Compatible with breastfeeding

Adverse effects: uterine or cervical perforation,

displacement, expulsion, exacerbation of pelvic infection, heavy menstrual bleeding, dysmenorrhoea, pain and bleeding and occasionally epileptic seizure or vasovagal attack on insertion.

Interaction with other medicines: There are no known significant interactions.

Levonorgestrel (LNG)

ATC code: G02BA03

LNG-releasing Intrauterine system Reservoir with 52 mg, LOU 2

Indications and dose:

Adult

Contraception, female: To be inserted into uterine cavity, within 7 days of onset of menstruation or immediately after 1st trimester abortion. If insertion occurs >7 days after menstrual bleeding has started, a barrier method of contraception must be used for 7 days unless the patient abstains from sexual intercourse.

Releases 20 micrograms of levonorgestrel/day over 5 years. May be removed and replaced with a new unit at any time during menstrual cycle.

Do not leave the system in place for more than 5 years.

Adolescent female, contraception:

Refer to adult dosing, not to be used prior to menarch

Contraindications: pregnancy, ischaemic heart disease, stroke, migraine with aura, thromboembolic disorders, unexplained vaginal bleeding, breast cancer, active viral hepatitis, severe liver disease, liver tumours.

Precautions: hypertension, heart disease, history of thromboembolism, epilepsy, migraine without aura, depression, gallbladder disease, diabetes mellitus, elevated cholesterol or triglycerides, breast nodules, breastfeeding (until weaning or for the first and less 6 months after birth)

Hepatic impairment: No dose adjustment necessary. Use is contraindicated in active hepatic disease or hepatic tumour.

Renal impairment: Dose adjustment not necessary.

Pregnancy: Contraindicated in pregnancy.

Breastfeeding: Infant risk cannot be ruled out.

Adverse effects: menstrual irregularities, headache, dizziness, lower abdominal pain, weight gain, acne, nausea, mood changes, breast tenderness, and loss of libido.

Interaction with other medicines (*indicates serious)

*Ritonavir, *tranexamic acid, *aprepitant, *artemether, anti-epileptics, darunavir, dexamethasone, efavirenz, griseofulvin, isotretinoin, mycophenolic acid, nevirapine, prednisolone, rifampicin, rifabutin, St. John's Wort, theophylline, *warfarin

Note:

- Inserted in the uterine cavity, to a depth of 6–9 cm, with the provider insertion device, should not be forced into the uterus.
- Advice patients to report symptoms of an ectopic pregnancy or a possible intrauterine pregnancy, symptoms of an infection, persistent or recurrent abnormal vaginal bleeding or amenorrhea

23.1.4. Contraceptive Implants

Etonorgestrel

ATC code: G03AC08

Releasing implant 68 mg (1 rod), LOU 2

Indications and dose:

Adult

Contraception, female, by subdermal implantation (no previous hormonal contraceptive) 1 implant inserted during first 5 days of cycle

Parturition or abortion in second trimester: 1 implant inserted between days 21–28 after delivery or abortion (if inserted after 28 days additional precautions necessary for next 7 days)

Abortion in first trimester: 1 implant inserted immediately.

Adolescent female, contraception:

Refer to adult dosing, not to be used prior to menarch

Contraindications: pregnancy, thromboembolic disorders, unexplained vaginal bleeding, breast cancer, active viral hepatitis, severe liver disease, liver tumours.

Precautions: hypertension, heart disease, history of thromboembolism, epilepsy, migraine without aura, depression, gallbladder disease, diabetes mellitus, elevated cholesterol or triglycerides, breast nodules, breastfeeding (until weaning or for the first and less 6 months after birth).

Hepatic impairment: contraindicated in hepatic impairment.

Renal impairment: Dose adjustment not necessary.

Pregnancy: Contraindicated in pregnancy.

Breastfeeding: Infant risk cannot be ruled out

Adverse effects: menstrual irregularities, headache, dizziness, lower abdominal pain, weight gain, acne, nausea, mood changes, breast tenderness, and loss of libido.

Interaction with other medicines (*indicates serious)

*Ritonavir, *tranexamic acid, aprepitant, *artemether, anti-epileptics, darunavir, dexamethasone, *efavirenz, *griseofulvin, isotretinoin, mycophenolic acid, nevirapine, prednisolone, rifampicin, rifabutin, St. John's Wort, sugammadex, theophylline, ulipristal

Note:

- Remove within 3 years of insertion, may be replaced with a new implant at the time of removal if continued contraceptive protection is desired. After ruling out pregnancy, timing of insertion is based on the patient's contraceptive history:

Levonorgestrel

ATC code: G03AC03

Implant 150 mg (2 × 75 mg rods), LOU 2

Two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg total); parenteral progestogen-only contraception (long term)

Indications and dose

Adult

Contraception (long term), female, 150-mg implant, subdermal: Insert 2 implants of 75 mg each; insert in non-dominant upper arm 6–8 cm above the elbow within the first 7 days of the menstrual cycle or immediately following first- or second-trimester abortion or delivery; use additional non-hormonal contraception if inserted at other time during menstrual cycle or later than 21 days after delivery

Adolescent: *Contraception*, female:
Refer to adult dosing; not to be used prior to menarche

Replace after5 years.

Contraindications: pregnancy, ischaemic heart disease, stroke, migraine with aura, thromboembolic disorders, unexplained vaginal bleeding, breast cancer, active viral hepatitis, severe liver disease, liver tumours.

Precautions: hypertension, heart disease, history of thromboembolism, epilepsy, migraine without aura, depression, gallbladder disease, diabetes mellitus, elevated cholesterol or triglycerides, breast nodules, breastfeeding (until weaning or for the first and less 6 months after birth).

Hepatic impairment: contraindicated in hepatic impairment.

Renal impairment: Dose adjustment not necessary.

Pregnancy: Contraindicated in pregnancy.

Breastfeeding: Infant risk cannot be ruled out.

Adverse effects: menstrual irregularities, headache, dizziness, lower abdominal pain, weight gain, acne, nausea, mood changes, breast tenderness, and loss of libido.

Interaction with other medicines (*indicates serious)

*Ritonavir, *tranexamic acid, aprepitant, *artemether, anti-epileptics, darunavir, dexamethasone, *efavirenz, griseofulvin, isotretinoin, mycophenolic acid, nevirapine, prednisolone, rifampicin, rifabutin, St. John's Wort, sugammadex, theophylline

Note:

» Implant insertion and removal requires specialist training

23.2. Ovulation Inducers

Clomifene (Clomiphene)

ATC code: G03GB02

Tablet, 50 mg (as citrate), LOU 4

Indications and dose

Adult

Anovulatory infertility, oral, female: 50 mg daily for 5 days, starting within 5 days of onset of menstruation, preferably on the second day, or at any time if cycles have ceased; a second course of 100 mg daily for 5 days may be given in the absence of ovulation; discontinue if ovulation does not occur after 3 courses of treatment, or if 3 ovulatory responses occur but pregnancy is not achieved

Paediatric: Safety and efficacy have not been established

Contraindications: hepatic disease, ovarian cysts, hormone dependent tumours or uterine bleeding of undetermined cause, pregnancy (exclude before treatment).

Precautions: visual disturbances (discontinue and initiate eye examination), ovarian hyperstimulation syndrome (discontinue treatment immediately), polycystic ovary syndrome (cysts may enlarge during treatment), uterine fibroids, ectopic pregnancy, incidence of multiple births increased (consider ultrasound monitoring), breastfeeding.

Hepatic impairment: Contraindicated in liver disease.

Renal impairment: Dose adjustment not necessary.

Pregnancy: Contraindicated in pregnancy.

Breastfeeding: Infant risk cannot be ruled out. Clomiphene may reduce breastfeeding.

Adverse effects: visual disturbances, ovarian hyperstimulation, hot flushes, abdominal discomfort, occasional nausea and vomiting, depression, insomnia, breast tenderness, headache, intermenstrual spotting, menorrhagia, endometriosis, convulsions, weight gain, rash, dizziness, hair loss.

Interaction with other medicines: No significant interactions.

Note:

» Advice patient that this drug can cause multiple pregnancies

Human Chorionic Gonadotropin (HCG)

ATC code: G03GA01

Injection 5,000-IU/vial, LOU 5

Indications and dose

Adult

Infertility in women with proven hypopituitarism or who have not responded to clomifene

Superovulation treatment for assisted conception (such as in vitro fertilization), female, by SC injection: 5,000 to 10,000 IU one day following last dose of menotropins

Hypogonadism (male), IM: 500 to 1000 IU three times a week for three weeks, then 500 to 1000 IU two times a week for three weeks OR

4000 IU three times a week for 6 to 9 months then 2000 units three times a week for three months

Paediatric

(male) for hypogonadism and cryptorchidism (non-KEML indication), IM:

Child ≥4years:

4000 IU three times a week for three weeks OR

5000 IU every other day for 4 injections OR

500 IU to 1000IU for fifteen injections over a period of six weeks OR

500 IU three times a week for four to six weeks

If unsuccessful, patients should be given an additional series using 1000IU starting one month later

Contraindications: Active thromboembolic disorders, ectopic pregnancy in previous 3 months, hypothalamus malignancy, mammary malignancy, ovarian enlargement or cyst (unless caused by polycystic ovarian disease), ovarian malignancy, pituitary malignancy, undiagnosed vaginal bleeding, uterine malignancy

Precautions: Acute porphyrias

Hepatic impairment: Dose adjustment not necessary

Renal impairment: Dose adjustment not necessary

Pregnancy: Contraindicated in pregnancy

Breastfeeding: Infant risk cannot be ruled out

Adverse effects: Common or very common Abdominal pain, fatigue, headache, nausea, ovarian hyperstimulation syndrome, vomiting, Breast pain, depression, diarrhea, irritability, restlessness, Rash, shock, thromboembolism

Interaction with other medicines: There are no known significant interactions.

Human Menopausal Gonadotropin (HMG)

ATC code: G03GA02

Injection, 75 IU, LOU 5

Indications and dose

Adult

Ovulation induction, female, by IM or SC injection induction: 150 IU for 5 days; subsequent doses are based on patient response; do not adjust dose more often than every 2 days and do not adjust by more than 75 to 150 IU per adjustment; maximum dose is 450 IU/day; maximum duration of treatment is 12 days

Assisted reproductive technologies, female, SC injection: Initial 225 units once daily beginning on cycle day 2 or 3; menotropins may be administered together with urofollitropin and the total initial dose of both products combined should not exceed 225 units (menotropins 150 units and urofollitropin 75 units, or menotropins 75 units and urofollitropin 150 units); adjust dose after 5 days based on ultrasound monitoring of ovarian response and/or measurement of serum estradiol levels; do not make additional adjustments more frequently than once every 2 days or by >150 units; maximum daily dose 450 units (of menotropins, or menotropins plus urofollitropin); treatment >20 days is not recommended; once follicular growth indicates an adequate ovarian response, administer hCG

Paediatric: Safety and efficacy have not been established

Contraindications: Hypersensitivity to menotropins or any component of the formulation, primary ovarian failure as indicated by a high follicle-stimulating hormone level, uncontrolled nongonadal endocrinopathies (e.g., thyroid, adrenal, pituitary), pituitary or hypothalamic tumors, sex hormone-dependent tumors of the reproductive tract and accessory organs, abnormal uterine bleeding of undetermined origin, ovarian cyst or enlargement not due to polycystic ovary syndrome, pregnancy.

Precautions: Hypersensitivity, Ovarian enlargement (The lowest effective dose should be used to decrease the risk of abnormal ovarian enlargement), Ovarian hyperstimulation syndrome, Ovarian torsion, Pulmonary effects, Thromboembolism

Hepatic impairment: Dose adjustment not necessary.

Renal impairment: Dose adjustment not necessary.

Pregnancy: Contraindicated in pregnancy.

Breastfeeding: Infant risk cannot be ruled out

Adverse effects: Common – injection site reactions, abdominal pain, nausea, abdominal fulness, headaches, multiple pregnancies. Others – tachycardia, ectopic pregnancy, dizziness, ovarian cyst, hemoperitoneum, ovarian neoplasm.

Interaction with other medicines: There are no known significant interactions.

Notes:

- To minimize risks, use only at the lowest effective dose. Monitor ovarian response with transvaginal ultrasound, concurrent measurement of estradiol levels may also be useful.
- These medications should only be used by physicians who are thoroughly familiar with infertility problems and their management.
- Multiple births may result from the use of these medications, advise patients of the potential risk of multi-foetal gestation and multiple births before starting the treatment.

Letrozole

ATC code: L02BG04

Tablets, 2.5 mg, LOU 4

Indications and dose

Adult

Ovulation induction in anovulatory females with polycystic ovary syndrome, female: 2.5 mg–5 mg daily for 5 days

Paediatric: Safety and effectiveness not established in paediatric patients.

Contraindications: Pregnancy, known hypersensitivity to letrozole

Precautions: Hypercholesterolemia, cirrhosis, severe hepatic impairment

Hepatic impairment: Reduce dose to 2.5 mg every other

day in severe impairment (child-pugh class C)

Renal impairment: Dose adjustment not necessary.

Pregnancy: Contraindicated in pregnancy.

Breastfeeding: Infant risk cannot be ruled out.

Adverse effects: Common oedema, sweating, hot flashes, athralgia, hypercholestereolemia, constipation, diarrhea, loss of appetite, nausea, vomiting, asthenia, dizziness, headache. Others - insomnia, somnolence, dyspnea, fatigue, heart failure, MI, pancytopenia, thromboembolic disorder, decreased bone density, bone fracture, pleural effusion, pulmonary embolism

Interaction with other medicines

Ceritinib, clarithromycin, methadone

23.3. Medicines For Treatment of Endometriosis

Danazol

ATC code: G03XA01

Capsule, 50 mg, LOU 4

Indications and dose

Adult

Endometriosis (as an alternative agent), female, orally: 200–800 mg daily in divided doses, adjusted according to response, usually for 3–6 months (maximum 9 months)

Paediatric: Safety and efficacy have not been established

Contraindications: undiagnosed genital bleeding, androgen dependent tumor, pregnancy, breastfeeding, porphyria, thromboembolic disease or active thrombosis, markedly impaired hepatic, renal, or cardiac function.

Precautions: seizure, migraine, conditions influenced by edema, diabetes mellitus

Hepatic impairment: Use is contraindicated in marked hepatic impairment.

Renal impairment: Use is contraindicated in marked renal impairment.

Pregnancy: Contraindicated in pregnancy

Breastfeeding: contraindicated in breastfeeding

Adverse effects: greasy skin, acne, voice changes and possibly signs of virilisation (when therapy should be stopped immediately), thrombophlebitis, cholestatic jaundice syndrome, seizure

Interaction with other medicines: Carbamazepine, cyclosporine, warfarin, simvastatin, tacrolimus

Notes:

- Amenorrhea and resolution of painful symptoms is indicative of efficacy.
- Drug causes sun-sensitivity, advice patient to use sunscreen.
- Recommend patient to use reliable contraception (nonhormonal) to avoid pregnancy during therapy and for several months post-treatment.

Dienogest

ATC code: G03DB08

Tablet, 2 mg, LOU 4

Indications and dose

Adult

Pelvic pain associated with endometriosis, female: 2 mg orally once daily for up to 16 months

Paediatric (female-post menarche)

Children ≥12 years and Adolescents, endometriosis, 2 mg orally once daily for up to 12 months.

Contraindications: hypersensitivity to dienogest or any component of the formulation, undiagnosed abnormal vaginal bleeding, active venous thromboembolic disorder, history of or current arterial and cardiovascular disease, diabetes mellitus with vascular involvement, history of or current severe hepatic disease where liver function tests remain abnormal, history of or current hepatic neoplasia (benign or malignant), known or suspected sex-hormone-dependent malignancy, ocular lesions due to ophthalmic vascular disease, such as partial or complete vision loss or defect in visual fields, current or history of migraine with focal aura, breastfeeding, known or suspected pregnancy.

Precautions: bleeding, breast cancer, carbohydrate intolerance, chloasma, Cholestatic jaundice, Hepatic tumors, ovarian cysts, pruritus, retinal vascular lesions, venous thromboembolism.

Hepatic impairment: Use is contraindicated in patients with a history of or current severe hepatic disease.

Renal impairment: Dose adjustment is not necessary.

Pregnancy: Use is contraindicated in pregnancy.

Breastfeeding: Use is contraindicated in breastfeeding women. The risk of thromboembolism may be increased immediately postpartum.

Adverse effects: Common - headache, depression, sleep disturbance, irritability, migraine, nervousness, acne, alopecia, breast discomfort, ovarian cyst, libido decreased, nausea, weight gain, abdominal pain, vaginal bleeding, weakness.

Interaction with other medicines (*indicates serious)

*Aprepitant, *efavirenz, *fosaprepitant, *griseofulvin, lamotrigine, *mycophenolate, *octreotide, thalidomide, warfarin, *barbiturates, benzodiazepines, *phenytoin, *rifamycin derivatives.

Note:

- Administer without regard to meals. If a dose is not absorbed due to vomiting and/or diarrhea within 3–4 hours of administration, repeat dose.

Goserelin

ATC code: L02AE03

Injection (depot, SC), 3.6 mg (as acetate), LOU 4

Indications and dose

Adult

Endometriosis, by SC injection: 3.6 mg every 28 days, maximum duration of treatment 6 months (do not repeat), to be administered into the anterior abdominal wall

Paediatric: Safety and efficacy has not been established.

Contraindications: Undiagnosed vaginal bleeding

Precautions: Depression, diabetes. Hypertension, patients with metabolic bone disease (decrease in bone mineral density can occur), polycystic ovarian disease.

Hepatic impairment: Use is contraindicated in marked hepatic impairment.

Renal impairment: Use is contraindicated in marked renal impairment.

Pregnancy: Contraindicated in pregnancy

Breastfeeding: contraindicated in breastfeeding

Adverse effects: Alopecia, arthralgia, bone pain, breast abnormalities, depression, glucose tolerance impaired, gynaecomastia, headache, heart failure, hot flush, hyperhidrosis, mood altered, MI, neoplasm complications, paraesthesia, sexual dysfunction, skin reactions, spinal cord compression, vulvovaginal disorders, weight increased. Hypercalcaemia, ureteral obstruction. Ovarian and fallopian tube disorders, pituitary haemorrhage, pituitary tumour, psychotic disorder

Abdominal cramps, body hair change, constipation, diarrhea, fatigue, hepatic function abnormal, interstitial pneumonia, muscle complaints, nausea, nervousness, peripheral oedema (when used for gynaecological conditions), premature menopause, pulmonary embolism, QT interval prolongation, sleep disorder, uterine leiomyoma degeneration, voice alteration, vomiting, vulvovaginal infection, withdrawal bleed

Interaction with other medicines: Bepridil, cisapride, dronedarone, mesoridazine, pimozide, piperaquine, saquinavir, sparfloxacin, terfenadine, thioridazine, ziprasidone, alfuzosin, amiodarone, amisulpride, amitriptyline, aripiprazole, atazanavir, azithromycin, bedaquiline, buprenorphine, ceritinib, chloroquine, chlorpromazine, ciprofloxacin, citalopram, clarithromycin, clozapine, domperidone, ebastine, erythromycin, efavirenz, escitalopram, famotidine, halofantrine, haloperidol, hydroxychloroquine, hydroxyzine, imipramine, levofloxacin, methadone, metronidazole, ocreotide, olanzapine, ondansetron, paroxetine, procainamide, quinine, risperidone, ritonavir, sevoflurane, sulpiride, tacrolimus, tamoxifen, zuclopenthixol

Notes:

- Conception and contraception: Non-hormonal, barrier methods of contraception should be used during entire treatment period.
- Pregnancy should be excluded before treatment; the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand. Rotate injection site to prevent atrophy and nodule formation.

Levonorgestrel (LNG)

ATC code: G02BA03

LNG-releasing intrauterine system, reservoir with 52 mg, LOU 4

Indications and dose

Adult

Pelvic pain associated with endometriosis, female: Insert into uterine cavity within 7 days of onset of menstruation or immediately after 1st trimester abortion; releases 20 micrograms of levonorgestrel/day over 5 years; may be removed and replaced with a new unit at anytime during menstrual cycle; do not leave any one system in place for 5 years

Paediatric

Used for other indications in postmenarche patients.

Contraindications: pregnancy, ischaemic heart disease, stroke, migraine with aura, thromboembolic disorders, unexplained vaginal bleeding, breast cancer, active viral hepatitis, severe liver disease, liver tumours.

Precautions: hypertension, heart disease, history of thromboembolism, epilepsy, migraine without aura, depression, gallbladder disease, diabetes mellitus, elevated cholesterol or triglycerides, breast nodules, breastfeeding (until weaning or for the first and less 6 months after birth)

Hepatic impairment: No dose adjustment necessary. Use is contraindicated in active hepatic disease or hepatic tumour.

Renal impairment: Dose adjustment not necessary

Pregnancy: Contraindicated in pregnancy.

Breastfeeding: Infant risk cannot be ruled out.

Adverse effects: menstrual irregularities, headache, dizziness, lower abdominal pain, weight gain, acne, nausea, mood changes, breast tenderness, and loss of libido

Interaction with other medicines: Refer to interactions on section 23.1.3.2 above

Notes:

- Inserted in the uterine cavity, to a depth of 6–9 cm, with the provider insertion device, should not be forced into the uterus.
- Advice patients to report symptoms of an ectopic pregnancy or a possible intrauterine pregnancy, symptoms of an infection, persistent or recurrent abnormal vaginal bleeding or amenorrhea

23.4. Medicines For Treatment of Fibroids

Goserelin

ATC code: L02AE03

Injection (depot, sc) 3.6 mg (as acetate), LOU 4

Adult

Indications and dose

Anaemia by SC injection: 3.6 mg every 28 days; maximum duration of treatment 3 months (to be administered into the anterior abdominal wall before surgery).

Paediatric: Safety and efficacy has not been established in children.

Contraindications, precautions, adverse effects, Interaction with other medicines and notes:

Refer to Goserelin in 23.3

Undiagnosed vaginal bleeding

Leuprorelin (Leuprolide)

ATC code: L02AE02

Injection (depot, sc) 3.75 mg (as acetate), LOU 4

Indications and dose

Adult

Reduce size of uterine fibroids and associated bleeding before surgery (specialist use only), by SC injection or IM injection: 3.75 mg every month usually for 3–4 months (maximum 6 months)

Paediatric

Used for other indications

Contraindications, precautions, adverse effects, Interaction with other medicines and notes:

Refer to Goserelin in 23.3

23.5. Medicines For Treatment of Abnormal Uterine Bleeding

Norethisterone

ATC code: G03DC02

Tablet, 5 mg, LOU 4

Indications and dose

Adult

Arrest dysfunctional uterine bleeding and menorrhagia, oral: 5 mg 3 times a day for 10 days

Prevent dysfunctional uterine bleeding and menorrhagia, oral: 5 mg twice daily, to be taken from day 19 to day 26 of cycle

Paediatric (female, post menarche):

Dysfunctional uterine bleeding, Oral: 2.5 to 10 mg once daily for 5 to 12 days each month

Contraindications: Avoid in patients with a history of liver tumours, breast cancer (unless progestogens are being used in the management of this condition), genital cancer (unless progestogens are being used in the management of this condition), history during pregnancy of idiopathic jaundice, history during pregnancy of pemphigoid gestationis (non-contraceptive indications), history during pregnancy of severe pruritus (non-contraceptive indications), acute porphyrias, severe arterial disease, undiagnosed vaginal bleeding

Precautions: Asthma, cardiac dysfunction, conditions that may worsen with fluid retention, diabetes (progestogens can decrease glucose tolerance—monitor patient closely), epilepsy, history of depression, hypertension, migraine, susceptibility to thromboembolism (particularly with high dose)

Hepatic impairment: Contraindicated in patients with hepatic tumors or acute liver disease.

Renal impairment: Dose adjustment is not necessary.

Pregnancy: Contraindicated in pregnancy

Breastfeeding: Present in breast milk. Exercise caution

Adverse effects: Menstrual cycle irregularities, appetite change, depression, fatigue, GI disorder, headaches, hypertension, libido disorder, nervousness, rash, weight change. Breast tenderness. Frequency not known Hepatic cancer, thromboembolism

Interaction with other medicines (*indicates serious)
*Ritonavir, *tranexamic acid, *penicillins, *aprepitant, *atazanavir betamethasone, *anti-epileptics, cephalosporins, cloxacillin, cyclosporine, darunavir, dexamethasone, doxycycline, *efavirenz, *isotretinoin, ocreotide, *rifampicin, * rifabutin, St. John's Wort, sugammadex, theophylline, diazepam, licorice, prednisolone, selegiline, warfarin

23.6. Uterotonics (Medicines Acting On the Uterus)

23.6.1. Oxytocics

Carbetocin

ATC code: H01BB03

Injection (heat-stable) 100 micrograms/mL, LOU 2

Indications and dose

Adult

Prevention of uterine atony after caesarean section, female, by slow IV injection: 100 micrograms for 1 dose, to be given over 1 minute; administer as soon as possible after delivery, preferably before removal of placenta

Paediatric

Safety and efficacy not established

Contraindications: Eclampsia, epilepsy, pre-eclampsia, hepatic impairment, renal impairment

Precautions: Asthma, cardiovascular disease (avoid if severe), hyponatraemia, migraine

Hepatic impairment: Dose adjustment not necessary.

Renal impairment: Dose adjustment not necessary.

Pregnancy: Contraindicated in pregnancy prior to delivery.

Breastfeeding: Present in breastmilk with minimal impact on breastfeeding infant.

Adverse Effects: Chest pain, chills, dizziness, dyspnea, feeling hot, flushing, headache, hypotension, nausea, pain, pruritus, taste metallic, tremor, vomiting, Hyperhidrosis, tachycardia

Interaction with other medicines (*indicates serious): Alfuzosin, barbiturates, BP lowering agents, *carboprost tromethamine, *dinoprostone, duloxetine, *misoprostol, nitroprusside, sildenafil, epoprostenol

Carboprost Tromethamine

ATC code: G02AD04

Solution for Injection, 250 micrograms per ml, LOU 2

Indications and dose

Adult

Postpartum haemorrhage due to uterine atony in patients unresponsive to ergometrine and oxytocin, by IM injection: 250 micrograms, repeated, if necessary, to be given at intervals of not less than 15 minutes. Total dose should not exceed 2 mg (8 doses)

Paediatric

Not applicable

Contraindications: Patients with known active cardiac, pulmonary, renal, and hepatic disease. Acute pelvic inflammatory disease. Should not be used where the patient is sensitive to carboprost tromethamine or to any of the excipients.

Precautions: Patients with history of anaemia, history of asthma, cardiovascular disease, diabetes, epilepsy, glaucoma, hypertension, hypotension, jaundice, pulmonary disease, raised intra-ocular pressure and uterine scars. Excessive dosage may cause uterine rupture.

Hepatic impairment: Manufacturer advises avoid in active hepatic disease.

Renal impairment: Manufacturer advises avoid.

Pregnancy: Contra-indicated in pregnancy.

Breastfeeding: There are no data on the excretion into breast milk for carboprost tromethamine

Adverse effects: Common or very common: chills, cough, diarrhea, headache, nausea, uterine disorders, vasodilation, and vomiting. Uncommon: Upper abdominal pain, asthma, back pain, breast tenderness, chest discomfort, dizziness, drowsiness, dry mouth, dyspnoea, eye pain, haemorrhage, hiccups, hyperhidrosis, hypertension, increased risk of infection, movement disorders, muscle complaints, paraesthesia, pelvic pain, respiratory disorders, septic shock, sleep disorder, syncope, tachycardia, altered taste, tinnitus, uterine injuries, vertigo, blurred vision. Frequency not known: Anxiety, asthenia, blepharospasm, choking sensation, palpitations, rash, thirst, throat complaints, thyrotoxic crisis

Interactions with other medicines: Carboprost can potentiate the effect of other oxytocics, concomitant use is not recommended.

Ergometrine

ATC code: G02AB03

Injection, 500 micrograms (as hydrogen maleate)/1-mL amp, LOU 2

Indications and dose

Adult

Prevention and treatment of postpartum haemorrhage (PPH), by IM injection: 200 micrograms when the anterior shoulder is delivered or immediately after birth

Excessive uterine bleeding, by slow IV injection: 250–500 micrograms when the anterior shoulder is delivered or immediately after birth

Adolescent: Follow adult dosing

Contraindications: induction of labour, first and second stages of labour, vascular disease, severe cardiac disease especially angina pectoris, severe hypertension, severe renal and hepatic impairment, sepsis, eclampsia.

Precautions: cardiac disease, hypertension, mild to moderate hepatic impairment, mild to moderate renal impairment, multiple pregnancy, porphyria.

Hepatic impairment: exercise caution in hepatic insufficiency.

Renal impairment: exercise caution in renal insufficiency.

Pregnancy: Ergonovine is used in the third stage of labor for the prevention or treatment of PPH and should not be used prior to delivery of the placenta.

Breastfeeding: breastfeeding is contraindicated when more than a single dose of ergonovine is administered to the postpartum mother. Administration of a single dose of ergonovine does not preclude a mother from nursing.

Adverse effects: nausea, vomiting, headache, dizziness, tinnitus, abdominal pain, chest pain, palpitations, dyspnoea, bradycardia, transient hypertension, vasoconstriction, stroke, MI and pulmonary oedema

Interaction with other medicines (*indicates serious)

*methoxamine, *phenylephrine, Ketamine, macrolides, HIV-protease inhibitors, *dopamine, *norepinephrine/epinephrine, anti-epileptics, *antifungals (azoles), dronedarone, beta-blockers, diltiazem, verapamil, crizotinib, cabergoline, pergolide, ticagrelor, *sumatriptan, *rifampicin, ceritinib, cobicistat, *bromocriptine, efavirenz, nevirapine, imatinib, St. John's Wort, grape juice, fluvoxamine, *lamivudine, *abacavir, nitroglycerine

Note:

» Injection requires transport by "cold chain" and refrigerated storage.

Mifepristone + Misoprostol

ATC code: G03XB51

Mifepristone 200 mg (1 tablet) + Misoprostol 200 micrograms (4 viginal tablets), in combi pack, LOU 2

Indications and dose

Adult

Medical termination of intrauterine pregnancy of up to 63 days gestation, oral: Mifepristone 200 mg as a single dose, followed 24–48 hours later (unless abortion already complete) by misoprostol 800 micrograms orally, buccally, or vaginally; observe individual for at least 6 hours (or until bleeding or pain at acceptable level), with follow-up visit 10–15 days later to verify complete expulsion

If treatment fails, it is essential that pregnancy be terminated by another method.

Adolescent: Follow adult dosing

Contraindications: uncontrolled severe asthma, suspected ectopic pregnancy (use other specific means of termination), chronic adrenal failure, porphyria.

Precautions: if treatment fails, it is essential that pregnancy is terminated by another method, asthma (avoid if severe), haemorrhagic disorders and anticoagulant therapy, prosthetic heart valve or history of endocarditis (antibacterial prophylaxis recommended), smokers aged over 35 years (increased risk of cardiovascular events), adrenal suppression

(may require treatment with a corticosteroid), not recommended in hepatic or renal impairment, breastfeeding, avoid use of acetylsalicylic acid (aspirin) and NSAIMs for analgesia.

Hepatic impairment: Not recommended in hepatic insufficiency

Renal impairment: Not recommended in renal failure

Pregnancy: Used to terminate pregnancy

Breastfeeding: mifepristone and misoprostol are present in breast milk. Breastfeeding is not recommended.

Adverse effects: Common - nausea, vomiting, GI cramps, uterine contractions, vaginal bleeding (sometimes severe), pain, dizziness, diarrhea, fever, weakness, chills. less commonly- hypersensitivity reactions including rash, urticaria, and facial oedema, septic shock, infection, breast tenderness, endometritis.

Interaction with other medicines (*indicates serious): *alfuzosin, *alprazolam, amiodarone, amlodipine, *antacids, *anticoagulants (e.g., warfarin), *aprepitant, aripiprazole, artemether lumefantrine, atorvastatin, *bromocriptine, *carbetocin, *corticosteroids, *ivabradine, *hormonal contraceptives, ketamine, *midazolam, *nimodipine, *oxytocin, *salmetrol, *quetiapine, *quinidine Aspirin, NSAIMs,* grapefruit juice

Note:

Used ONLY for medical termination of pregnancy and recommmended within the first nine weeks of gestation for medical indications as provide for in the Kenyan constitution article 26

Misoprostol

ATC code: G02AD06

Tablet, 200 micrograms, LOU 2,

Vaginal tablet, 25 micrograms, LOU 2

Indications and dose

Adult

Induction of labour, by vagina: Initially 25 micrograms, repeated after 6 hours if necessary; if still no response, increase to 50 micrograms every 6 hours for up to 4 doses

Medical termination of intrauterine pregnancy of up to 63 days gestation: Refer to 23.6.1.3

Adolescent: Follow adult dosing

Contraindications:

Induction of labour: Placenta praevia or unexplained vaginal bleeding during pregnancy, ruptured membranes, major cephalopelvic disproportion or foetal malpresentation, history of caesarean section or major uterine surgery, untreated pelvic infection, foetal distress, grand multiparas and multiple pregnancy, history of difficult or traumatic delivery.

Precautions: induction of labour, conditions where hypotension might precipitate severe complications (for example, cerebrovascular disease or cardiovascular disease).

Medical termination of pregnancy. History of caesarean section or major uterine surgery, grand multiparas (risk of rupture).

Adverse effects: uterine hyperstimulation, uterine rupture, foetal distress, less commonly in obstetric setting diarrhoea, abdominal pain, dyspepsia, flatulence, nausea and vomiting, rash, dizziness.

Hepatic impairment: Dose adjustment not necessary

Renal impairment: Dose adjustment not necessary.

Pregnancy: Use is contraindicated during pregnancy

Breastfeeding: Present in breast milk. Use caution when breastfeeding.

Interaction with other medicines: *Refer to mifepristone + misoprostol above*

Notes:

- For medical termination of pregnancy, oral tablets may be administered vaginally if a suitable vaginal preparation is not available, for induction of labour, low-dose vaginal tablets should be used, but if these are not available, 100-microgram oral tablets can be divided to the required dose and administered vaginally.
- Should it be necessary to continue induction of labour with oxytocin, administration of oxytocin should be avoided within 8 hours of using misoprostol.

Oxytocin

ATC code: H01BB02

Injection, 10 IU/1-mL amp, LOU 2

Indications and dose

Adult

Induction of labour, by IV infusion: Initially 0.001–0.002 IU/min increased in 0.001–0.002 IU/min increments at intervals of 30 minutes until up to 3–4 contractions occur every 10 minutes; maximum rate 0.02 IU/min

Prevention of PPH, by IM injection: 10 IU when the anterior shoulder is delivered or immediately after birth

Prevention of PPH, by slow IV injection: 5 IU when the anterior shoulder is delivered or immediately after birth

Treatment of PPH: By slow IV injection5–10 IU, or by IM injection 10 IU, followed in severe cases by a total of 40 IU by IV infusion, at a rate of 0.02–0.04 IU/min, which should be started after the placenta is delivered

Adolescent: Follow adult dosing

Contraindications: hypertonic uterine contractions, mechanical obstruction to delivery, foetal distress, any condition where spontaneous labour or vaginal delivery is inadvisable, avoid prolonged administration in oxytocin-resistant uterine inertia, in severe pre-eclamptic toxaemia, or in severe cardiovascular disease, major cephalopelvic disproportion.

Precautions: induction or enhancement of labour in presence of borderline cephalopelvic disproportion (avoid if significant), mild to moderate pregnancy-associated hypertension or cardiac disease, age over 35 years, history of low-uterine segment caesarean section, avoid tumultuous labour if foetal death or

meconium-stained amniotic fluid (risk of amniotic fluid embolism) occurs, water intoxication and hyponatraemia (avoid large volume infusions and restrict fluid intake), caudal block anaesthesia (risk of severe hypertension due to enhanced vasopressor effect of sympathomimetics)

Hepatic impairment: Dose adjustment not necessary.

Renal impairment: Dose adjustment not necessary

Pregnancy: used for induction of labour

Breastfeeding: oxytocin may disrupt initiation of breastfeeding.

Adverse effects: Frequency not defined - uterine spasm, and uterine hyperstimulation (usually with excessive doses, may cause foetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions, soft-tissue damage, or uterine rupture), water intoxication and hyponatraemia (with high doses and large-volume infusions), nausea, vomiting, arrhythmias, rash and anaphylactoid reactions

Interaction with other medicines (*indicates serious)

*Dinoprostone, Ephedrine (nasal and systemic), *carboprost tromethamine, *misoprostol, succinyl choline.

Notes:

- Careful monitoring of foetal heart rate and uterine motility is essential for dose titration (avoid bolus IV injection during labour), discontinue immediately in uterine hyperactivity or foetal distress.
- Prolonged IV administration at high doses with large volume of fluid (for example, in inevitable or missed abortion, or in PPH may cause water intoxication with hyponatraemia. To avoid this, use electrolyte-containing diluent (not glucose), increase oxytocin concentration to reduce fluid, and restrict fluid intake oral, monitor fluid, and electrolytes.

Prostaglandin E2

ATC code: G02AD02

Vaginal tablet, 3 mg, LOU 4

Indications and dose

Adult

Initiation and/or cervical ripening in patients at or near term in whom there is a medical or obstetrical indication for the induction of labor: Insert high in to posterior formix, 3 mg, followed after 6–8 hours by 3 mg if labour is not established; maximum 6 mg

Adolescent: Follow adult dosing

Contraindications: hypersensitivity to prostaglandins, foetal distress, unexplained vaginal bleeding during this pregnancy, acute pelvic inflammatory disease, uterine fibroids, and cervical stenosis.

Precautions: cervicitis, infected endocervical lesions, acute vaginitis, compromised (scarred) uterus or history of asthma, hypertension or hypotension, epilepsy, diabetes mellitus, anemia, jaundice, cardiovascular, renal, or hepatic disease.

Hepatic impairment: Dose adjustment not necessary

Renal impairment: Dose adjustment not necessary

Pregnancy: Increase in uterine tone may increase risk of adverse events to fetus.

Breastfeeding: May inhibit breastfeeding. Foetal risk cannot be ruled out.

Adverse effects: vomiting, diarrhea, nausea, fever. Less common – headache, bradycardia, fever, back pain, bronchospasm, cardiac arrhythmia, chills, cough, dizziness, dyspnea, flushing, hot flushes, hypotension, pain, shivering, syncope, tightness of the chest, vasomotor and vasovagal reactions, wheezing.

Interaction with other medicines (*indicates serious):

*Oxytocin, *ergometrine, *ephedrine, *carbetocin, *carboprost tromethamine.

Note:

- A dosing interval of at least 30 minutes is recommended for the sequential use of oxytocin following the removal of the prostaglandin E2 vaginal insert. A 6 hours interval is needed between its insertion and initiation of oxytocin infusion.

23.7. Anti-Oxytocics (Tocolytics)

Salbutamol

ATC code: R03CC02

Injection, 500 micrograms (as sulphate)/mL (5-mL amp), LOU 4

Indications and dose

Adult

Arrest uncomplicated premature labour between 24 and 33 weeks gestation: 10 micrograms/min, gradually increased to maximum of 45 micrograms/min until contractions have ceased, then gradually reduced; or by IV or IM injection, 100–250 micrograms repeated according to patient's response; subsequently oral 4 mg every 6–8 hours

Adolescent: Follow adult dosing

Contraindications: cardiac disease, eclampsia and severe preeclampsia, intra-uterine infection, antepartum haemorrhage (requires immediate delivery), placenta praevia, cord compression, not used in first or second trimesters.

Precautions: suspected cardiac disease, hypertension, hyperthyroidism, hypokalaemia, diabetes mellitus, mild to moderate pre-eclampsia.

Adverse effects: nausea, vomiting, flushing, sweating, tremor, hypokalemia, tachycardia, muscle cramps, palpitation and hypotension, increased tendency to uterine bleeding, pulmonary oedema, chest pain or tightness, arrhythmias, headache.

Interaction with other medicines: Corticosteroids, diuretics, theophylline.

Note:

- The patient's state of hydration and heart rate should be monitored carefully.

Terbutaline Sulphate

ATC code: R03CC03

Solution for Injection, 0.5 mg / mL, 1 mL, 5 mL, LOU 4

Indications and dose

Adult

Uncomplicated premature labour (between 22 and 37 weeks of gestation) (specialist supervision in hospital), by IV infusion: Initially 5 micrograms/minute for 20 minutes, then increased in steps of 2.5 micrograms/minute every 20 minutes until contractions have ceased (more than 10 micrograms/minute should seldom be given— 20 micrograms/minute should not be exceeded), continue for 1 hour, then reduced in steps of 2.5 micrograms/minute every 20 minutes to lowest dose that maintains suppression (maximum total duration 48 hours).

Paediatric: Not applicable.

Contraindications: Abruptio placenta, antepartum haemorrhage, cord compression, eclampsia, history of cardiac disease, intra-uterine fetal death, intra-uterine infection, placenta praevia, pulmonary hypertension, severe pre-eclampsia, significant risk factors for myocardial ischaemia, threatened miscarriage

Precautions: Mild to moderate pre-eclampsia, thyrotoxicosis, suspected cardiovascular disease (should be assessed by a cardiologist before initiating therapy for uncomplicated premature labour)

Hepatic impairment: *No guidelines for dosage adjustment in patients with hepatic impairment are* available

Renal impairment:

- CrCl > 50 ml/min: No dosage adjustment is needed.
- CrCl 10-50 ml/min: Give 50% of the usual systemic dose given at the normal dosage interval.
- CrCl < 10 ml/min: Avoid use

Pregnancy: Although no teratogenic effects have been observed in animals or in patients, terbutaline sulphate should be administered with caution during the first trimester of pregnancy.

Breastfeeding: Secreted into breast milk, but any effects on the infant are unlikely at therapeutic doses. Transient hypoglycaemia has been reported in newborn preterm infants after maternal beta2-agonist treatment.

Adverse effects: Common or very common: Hypokalaemia, hypotension, muscle spasms, nausea. Rare or very rare: myocardial ischemia, vasodilation, with parenteral use lactic acidosis and pulmonary oedema. Frequency not known: Angioedema, anxiety, abnormal behavior, bronchospasm, circulatory collapse, oral irritation, skin reactions, sleep disorder, throat irritation. With parenteral use: akathisia and bleeding tendency.

Interactions with other medicines:

- Beta-blocking agents may partially or totally inhibit the effect of beta-stimulants
- Halogenated anaesthetics: owing to the additional antihypertensive effect, there is increased uterine inertia with risk of haemorrhage; in addition, serious ventricular rhythm disorders due to increased cardiac reactivity, have been reported on interaction with halogenated anaesthetics.
- Corticosteroids: Systemic corticosteroids are frequently given during premature labour to enhance foetal lung development. There have been reports of pulmonary oedema in women concomitantly administered with beta-agonists and corticosteroids. Corticosteroids are also known to increase blood glucose and can deplete serum potassium; therefore, concomitant administration should be undertaken with caution and patient continuously monitored for hyperglycaemia and hypokalaemia.
- Anti-diabetics: The administration of beta-agonists is associated with a rise of blood glucose, which can be interpreted as an attenuation of anti-diabetic therapy. Anti-diabetic therapy may need to be adjusted.
- Potassium depleting agents: Owing to the hypokalaemic effect of beta-agonists, concurrent administration of serum potassium depleting agents known to exacerbate the risk of hypokalaemia, such as diuretics, digoxin, methyl xanthines and corticosteroids, should be administered cautiously after careful evaluation of the benefits and risks with special regard to the increased risk of cardiac arrhythmias arising as a result of hypokalaemia

Notes:

- **Monitoring Requirements:** In uncomplicated premature labour it is important to monitor blood pressure, pulse rate (should not exceed 120 beats per minute), ECG (discontinue treatment if signs of myocardial ischaemia develop), blood glucose and lactate concentrations, and the patient's fluid and electrolyte status (avoid over-hydration—discontinue drug immediately and initiate diuretic therapy if pulmonary oedema occurs).

23.8. Other Medicines Administered to the Mother

Dexamethasone

ATC code: H02AB02

Injection, 4 mg (as disodium phosphate)/mL, LOU 4

Indications and dose

Adult

Reduction of neonatal morbidity and mortality from preterm delivery, IM: 6 mg every 12 hours for 4 doses; first dose may be administered even if ability to give second dose is unlikely based on clinical scenario

Adolescent: Follow adult dosing

Contraindications: hypersensitivity to dexamethasone, sulphites, systemic fungal infection.

Precautions: latent or active amoebiasis, cerebral malaria, cirrhosis, concomitant use with vaccines, GI disorders, hypertension, myasthenia gravis, renal insufficiency, TB.

Hepatic impairment: Dose adjustment not necessary.

Renal impairment: Dose adjustment not necessary.

Pregnancy: Avoid chronic use of high doses in pregnancy.

Breastfeeding: Single doses are compatible with breastfeeding. Infant risk cannot be ruled out.

Adverse effects: Body fluid retention, hyperglycemia

Interaction with other medicines (*indicates serious):

Artemether, *Aprepitant, *Desmopressin, *Disulfiram, Praziquantel, Rilpivirine, Rotavirus vaccine, Amiodarone, Balofloxacin, Besifloxacin, Ciprofloxacin, Dronedarone, Enoxacin, Fentanyl, Flumequine, Gatifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Nifedipine, Norfloxacin, Ofloxacin, Sparfloxacin, Aspirin, Atracurium, Capsofungin, Licorice, Pancuronium, Phenobarbital, Vecuronium, Warfarin

Tranexamic Acid

ATC code: B02AA02

Injection, 100 mg/mL (10 amp), LOU 2

Indications and dose

Adult

Reduce hemorrhage in pregnant women with PPH: Administer at a fixed dose of 1 g in 10 mL (100 mg/mL) IV at 1 mL per minute (i.e., administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes

Adolescent: Follow adult dosing

Contraindications:

Tranexamic acid should not be used in women with a clear contraindication to antifibrinolytic therapy, including tranexamic acid (e.g., a known thromboembolic event during pregnancy, history of coagulopathy, active intravascular clotting, or known hypersensitivity to tranexamic acid.

Precautions:

Inadvertent intrathecal administration has resulted in serious adverse reactions including seizures and cardiac arrhythmias, cardiovascular, thrombosis and thromboembolism, venous, arterial have been reported with IV administration

Immunologic, anaphylaxis and severe allergic reactions have been reported

Neurologic, convulsions have been reported with IV formulations

Hepatic impairment: Dose adjustment is not necessary

Renal impairment: Dose adjustment necessary in reduced renal function

Pregnancy: No evidence of teratogenicity in animal studies. Use if potential benefits outweigh risks.

Breastfeeding: Present in breast milk. It does not pose significant risk to breastfeeding infant.

Adverse effects: Allergic dermatitis, dizziness, hypotension, nausea, vomiting, diarrhea

Interaction with other medicines (*indicates serious):

*Anti-inhibitor coagulant complex, *estrogen derivatives, Factor IX complex, *hormonal contraceptives, *tretinoin, Chlorpromazine

Notes:

- WHO recommends early use of IV tranexamic acid within 3 hours of birth in addition to standard care for women with clinically diagnosed PPH following vaginal birth or caesarean section.
- Administration of tranexamic acid should be considered as part of the standard PPH treatment package and be administered as soon as possible after onset of bleeding and within 3 hours of birth. Tranexamic for PPH treatment should not be initiated more than 3 hours after birth.
- Tranexamic acid should be used in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes.
- Tranexamic acid should be administered via an IV route only for treatment of PPH.

23.9. Medicines Administered to the Neonate

Caffeine Citrate

ATC code: N06BC01

Sterile solution for IV or oral use, 20 mg/mL (equivalent to 10 mg caffeine base/mL), LOU 4

Sterile solution for IV or oral use, 10 mg/mL (equivalent to 5 mg caffeine base/mL), LOU 4

Indications and dose

Paediatric

Neonatal apnoea in preterm infants, oral or IV

Neonate: 20 mg/kg as a loading dose, then 5 mg/kg once daily, starting 24 hours after loading dose; maintenance dose may be increased by 5 mg/kg every 24 hours to a maximum of 20 mg/kg/day, unless adverse effects develop; continue 4–5 days after cessation of apnoea

Contraindications: Hypersensitivity to caffeine or citrate.

Precautions: Cardiovascular disorders, gastro-oesophageal reflux, seizure disorders, renal impairment and hepatic impairment.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Common: Gastric irritation (oral administration) including nausea and vomiting, feeding intolerance, irritability, agitation, hyperglycaemia or hypoglycaemia, tachycardia, diuresis.

rarely acidosis, disseminated intravascular coagulation, haemorrhage, lung oedema, gastritis, renal failure, retinopathy of prematurity, and sepsis.

Lethargy (physical sign of withdrawal), excessive CNS stimulation.

Rare: Acidosis, necrotizing enterocolitis.

Interaction with other medicines:
Ciprofloxacin, Theophylline:

Notes:

- All doses are expressed as caffeine citrate.
- Caffeine citrate 2 mg = caffeine base 1 mg.
- Caffeine citrate, a respiratory stimulant, is used for neonatal apnoea in preterm infants (born less than 35 weeks gestational age and under 2 kg). It is preferred over theophylline, as caffeine has a better safety profile and does not require routine drug level monitoring. Other causes of neonatal apnoea should be sought and treated before treatment with caffeine is started (e.g., sepsis, hypothermia, hypoglycaemia, hypoxaemia, anaemia, seizures).
- Oral liquid may be given without regard to feeds.
- Injectable formulation (caffeine citrate) may be given orally if necessary.
- Administration For IV administration, infuse loading dose over at least 30 minutes and maintenance dose over at least 10 minutes. May be given undiluted or diluted with 5% dextrose to caffeine citrate 10 mg/mL.
- Discoloured or cloudy solutions for injection should not be used.
- The pharmacological actions of caffeine in apnoea includes stimulation of the medullary respiratory centre, increased sensitivity to carbon dioxide and enhanced diaphragmatic contractility.

Chlorhexidine

ATC code: D08AC02

Gel, 7.1% (as digluconate) 20 g tube, LOU 2

Indications and dose

Paediatric

Newborn: Prophylaxis of omphalitis/umbilical cord care; apply amount necessary to cover the wound

Contraindication: Hypersensitivity to chlorhexidine gluconate or any other component of the product

Precautions:

Aqueous solutions are susceptible to microbial contamination, use sterilized preparation or freshly prepared solution and avoid contamination during storage or dilution, instruments with cemented glass components (avoid preparations containing surface active agents), irritant (avoid contact with middle ear, eyes, brain and meninges), not for use in body cavities, alcoholic solutions not suitable before diathermy, syringes and needles treated with chlorhexidine (rinse thoroughly with sterile water or saline before use), inactivated by cork (use glass, plastic or rubber closures), ethanol-based solutions are flammable.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Skin sensitivity and irritation.

Corneal damage due to accidental contact, hypersensitivity reactions.

Interaction with other medicines: Inactivated by soaps and other anionic materials. Activity may be reduced in the presence of suspending agents, insoluble powders or compounds.

Insoluble salts may form in hard water.

Notes:

- Chlorhexidine is a representative disinfectant and antiseptic. Various agents can serve as alternatives.
- Most active against Gram-positive bacteria, with some Gram-negative activity. Spores and hydrophilic viruses are resistant. Chlorhexidine gluconate may be mixed with quaternary ammonium compounds for broader antimicrobial activity.
- This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.
- Dilution and administration. According to manufacturer's directions.

Ibuprofen

ATC code: C01eB16

Solution for injection. 5 mg/mL, LOU 5

Indications and dose

Paediatric

Closure of ductus arteriosus, IV

Neonate: 10 mg/kg as a single dose, followed by two doses of 5 mg/kg after 24 and 48 hours; course may be repeated after 48 hours if necessary

Contraindications: Life-threatening infection, active bleeding especially intracranial

or GI, thrombocytopenia or coagulation defects, marked unconjugated hyperbilirubinaemia, known or suspected necrotizing enterocolitis, pulmonary hypertension, severe renal failure, hepatic failure or cardiac failure.

Precautions: May mask symptoms of infection, monitor for bleeding, monitor GI function, cardiac disease, volume depletion, dehydration, coagulation defects, allergic disorders, renal impairment, deterioration in renal function possibly leading to renal failure may occur, hepatic impairment.

Hepatic impairment: Avoid in severe liver disease.

Renal impairment: Use lowest effective dose and monitor renal function. Sodium and water retention

may occur. Deterioration in renal function possibly leading to renal failure may occur. Avoid if possible, in severe impairment.

Adverse effects: Gastro-oesophageal reflux, gastritis, hypoglycaemia, hypocalcaemia, elevated creatinine, anaemia, apnoea, sepsis.

Rash, urticaria, photosensitivity, renal impairment, ileus, feeding problems, GI perforation, necrotizing enterocolitis.

Angioedema, bronchospasm, hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (SJS), toxic epidermal necrolysis (Lyell syndrome), colitis, aseptic meningitis.

Interaction with other medicines (*indicates serious):

* Acetylsalicylic acid: avoid concomitant use (increased adverse effects).

* Ciclosporin: increased risk of nephrotoxicity.

* Ciprofloxacin: possibly increased risk of seizures.

Dexamethasone: increased risk of GI bleeding and ulceration.

Digoxin: possible exacerbation of heart failure, reduced renal function and increased plasma

digoxin concentration.

Enalapril: antagonism of hypotensive effect, increased risk of renal impairment. Furosemide: risk of nephrotoxicity of ibuprofen increased antagonism of diuretic effect. Heparin: possibly increased risk of bleeding.

Hydrocortisone: increased risk of GI bleeding and ulceration.

* Levofloxacin: possibly increased risk of seizures.

* Methotrexate: excretion of methotrexate reduced (increased risk of toxicity).

* Ofloxacin: possible increased risk of seizures.

Penicillamine: possible increased risk of nephrotoxicity.

* Phenytoin: effect of phenytoin possibly enhanced.

Prednisolone: increased risk of GI bleeding and ulceration.

Propranolol: antagonism of hypotensive effect.

Ritonavir: plasma concentration possibly increased by ritonavir.

Spironolactone: risk of nephrotoxicity of ibuprofen increased, antagonism of diuretic effect, possibly increased risk of hyperkalaemia.

* Warfarin: anticoagulant effect possibly enhanced. Zidovudine: increased risk of haematological toxicity.

Notes:

- Administration: By slow IV injection over 15 minutes, preferably undiluted.
- May be diluted with glucose 5% or sodium chloride 0.9%.
- This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Prostaglandin E2

ATC code: G02AD02

Solution for injection, prostaglandin E2: 1 mg/mL, LOU 5

Indications and dose

Paediatric

Temporary maintenance of patency of the ductus arteriosus in infants with congenital heart malformation dependent on ductal shunting for oxygenation/perfusion, continuous IV infusion

Neonate: Initially 5–10 nanograms/kg/min, adjust according to *response* in 5 nanograms/kg/min increments to 20 nanograms/kg/min; doses up to 100 nanograms/kg/min have been used but are associated with increased adverse effects.

Contraindications: Hepatic impairment, renal impairment.

Precautions: History of haemorrhage, avoid in hyaline membrane disease, monitor arterial oxygenation, heart rate, temperature and blood pressure in arm and leg, facilities for intubation and ventilation must be immediately available.

Hepatic impairment: Manufacturer advises to avoid in hepatic impairment.

Renal impairment: Manufacturer advises to avoid in renal impairment.

Adverse effects: Nausea, vomiting, diarrhoea, flushing, bradycardia, hypotension, cardiac arrest, respiratory depression and apnoea (particularly with high doses and in low-birth- weight neonates).

Bronchospasm, fever, raised WBC count, shivering, local reactions, erythema. Rare Following prolonged use (greater than 5 days), gastric outlet obstruction and cortical hyperostosis have been reported.

Interaction with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

- Dilute to a concentration of 1 microgram/mL with glucose 5% or sodium chloride 0.9%.
- Injection solution can be given orally, diluted with water.
- Prostaglandin E2 is also referred to as dinoprostone.

Sildenafil

ATC code: GO4BE03

Powder for oral liquid, 10 mg/mL, LOU 5

Indications and dose

Paediatric

Pulmonary hypertension, Oral:

Neonate: 0.25 mg/kg/dose every 6hours **or** 0.5mg/kg/dose every 8 hours, titrate as needed, maximum reported dose range: 1 to 2 mg/kg/dose every 6 to 8 hours

Contraindication: Hereditary degenerative retinal disorders, history of non- arteritic anterior ischaemic optic neuropathy. recent history of MI, recent history of stroke

Precautions: When used for pulmonary arterial hypertension Hypotension (avoid if systolic blood pressure below 90 mmHg), intravascular volume depletion, pulmonary veno- occlusive disease.

Adverse effects: Alopecia, anaemia, anxiety, Cough, diarrhea, dizziness, fluid retention, GI discomfort, GI disorders, headaches, increased risk of infection, insomnia, nasal complaints, nausea, night sweats, pain, skin reactions, tremor, vasodilation and vision disorders

Arrhythmias, chest pain, drowsiness, dry eye, dry mouth, eye discomfort, eye disorders, eye inflammation, fatigue, feeling hot, gynecomastia, hemorrhage, hypertension, hypotension, myalgia, numbness, palpitations, sinus congestion, tinnitus, vertigo and vomiting

Acute coronary syndrome, arteriosclerotic retinopathy, cerebrovascular insufficiency, glaucoma, haematospermia, hearing impairment, irritability, optic neuropathy (discontinue if sudden visual impairment occurs), oral hypoaesthesia, priapism, retinal occlusion, scleral discolouration, seizure, SCARs, sudden cardiac death, syncope and throat tightness

Interaction with other medicines (*indicates serious)

*Amprenavir, *Atazanavir, *Darunavir, *Indinavir, *Lopinavir, *Ritonavir, *Saquinavir

Cannabis, Clarithromycin, Fluconazole, Itraconazole, Voriconazole, Ciprofloxacin, Erythromycin, Ketoconazole, prazocin

Notes:

» Higher than recommended doses should not be used in paediatric patients with PAH

Surfactant

ATC code: R07AA02

Suspension for intratracheal instillation, 25 mg/mL or 80 mg/mL, LOU 5

Indications: Treatment and prophylaxis of respiratory distress syndrome (hyaline membrane disease) in preterm neonates

Paediatric

Beractant

Treatment of respiratory distress syndrome (hyaline membrane disease) in preterm neonates, endotracheal tube

Neonate: 100 mg/kg (equivalent to a volume of 4 mL/kg) preferably within 8 hours of birth. Dose may be repeated within 48 hours at intervals of at least 6 hours for up to four doses. Administer dose of beractant in four 1 mL/kg aliquots with infant in different position for each aliquot. Ventilator support or inspired oxygen may need to be temporarily increased.

Prophylaxis of respiratory distress syndrome (hyaline membrane disease) in preterm neonates, endotracheal tube

Neonate: 100 mg/kg as soon as possible after birth. Up to four doses may be administered in the first 48 hours of life, not more frequently than 6 hours apart. Administer in four 1 mL/kg aliquots with infant in different position for each aliquot. Ventilator support or inspired oxygen may need to be temporarily increased.

Bovine lipid extract surfactant

Respiratory distress, rescue treatment, intratracheal

Neonate: 5ml/kg/dose (equals phospholipids 135mg/kg/dose); may repeat if needed to a maximum of 4 doses within the first five days of life

Poractant alfa

Treatment of respiratory distress syndrome (hyaline membrane disease) in preterm neonates, endotracheal tube

Neonate: 100–200 mg/kg (equivalent to a volume of 1.25–2.5 mL/kg); if still intubated, 2 further doses of 100 mg/kg may be given at 12-hour intervals; maximum total dose 400 mg/kg.

Prophylaxis of respiratory distress syndrome (hyaline membrane disease) in preterm neonates, endotracheal tube

Neonate: 100–200 mg/kg soon after birth (preferably within 15 minutes); further doses of 100 mg/kg may be repeated 6–12 hours later and after a further 12 hours if still intubated; maximum total dose is 400 mg/kg; administer in two aliquots with infant in different position for each aliquot to ensure delivery to the two main bronchi; ventilator support or inspired oxygen may need to be temporarily increased

Contraindications: There are no contraindications to the use of surfactant in preterm neonates.

Precautions: Continuous monitoring is required to avoid hyperoxaemia caused by rapid

improvement in arterial oxygen concentration.

Hepatic impairment: No dosage adjustment necessary.

Renal impairment: No dosage adjustment necessary.

Adverse effects: Rare: Pulmonary haemorrhage has been rarely associated with pulmonary surfactants, especially in more preterm neonates. Obstruction of the endotracheal tube by mucus secretions has been reported.

Interaction with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

- Beractant and poractant alfa are not the same product. Consult product information for more details on administration.
- Refrigerate and protect from light.
- Do not shake. Gently swirl to ensure complete mixing of suspension.
- Prior to administration, warm by standing at room temperature for 20 minutes or hold in hand for 8 minutes. Artificial warming methods should not be used. Do not use or return vials to the refrigerator if they have been at room temperature for 8 hours or more (beractant) or 24 hours or more (poractant alfa). Vials may only be returned to the refrigerator once after having reached room temperature.
- Suction infant prior to administration.
- Continuous monitoring of heart rate and transcutaneous oxygen saturation should be performed during administration.
- Pneumothorax has occurred due to sudden changes in pulmonary compliance if ventilator settings are not appropriately adjusted.
- Avoid suctioning the endotracheal tube for 2 hours post-administration unless there are clear signs of airway obstruction.
- Surfactant is available as beractant (bovine lung surfactant providing phospholipid 25 mg/mL) and poractant alfa (porcine lung surfactant providing phospholipid 80 mg/mL).

24.Dialysis Solutions

Intraperitoneal Dialysis Solution (CAPD)

ATC code: B05DA

Solution, LOU 4

Indications and dose

Adult

Correct electrolyte imbalance and fluid overload and remove metabolites in renal failure: Individualized according to clinical condition and based on blood results. Initial dialysis ideally delayed for 2 weeks after insertion of catheter. Start with low volumes, e.g., 10 mL/kg and gradually increase to maximum 50 mL/kg (1100 mL/m2) to avoid creating leak at catheter exit site.

Paediatric

Individualized according to clinical condition and based on blood results.

Contraindications: Abdominal sepsis, severe inflammatory bowel disease.

Precautions: Previous abdominal surgery, care required with technique to reduce risk of infection, some drugs may be removed by dialysis.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Infection (including peritonitis), hernia, haemoperitoneum, hyperglycaemia, protein malnutrition, blocked catheter, pain on filling (related to acidic pH of some dialysis solutions), hypokalaemia with aggressive dialysis.

Interaction with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

- Warm dialysis solution to body temperature before use.
- Increasing concentrations of glucose allow increasing efficiency of fluid removal (e.g., 1.5%, 2.3%, 4.5%). Lower concentrations (e.g., 1.5%) are gentler and appropriate for maintenance. High osmolality solutions (e.g., 4.25%) can be used intermittently for severe fluid overload.
- Solutions containing 1.5% of glucose may be used in the management of acute renal failure, uncontrolled hyperkalemia or oliguria in the presence of a rapid catabolic rate.
- Solutions containing decreased sodium concentration are used to prevent post-dialysis hypernatraemia.
- Solutions containing acetate are used in patients with impaired lactate metabolism and also in patients with hepatic dysfunction or impaired tissue perfusion.
- Solutions containing decreased magnesium concentrations (i.e. 0.5 meq/L) are used for patients with hypermagnesaemia or in patients in whom increased oral magnesium intake is desirable.
- Commercially available solutions do not usually contain potassium as the solutions are frequently used for removing potassium in patients with hyperkalaemia. Potassium may be added to the dialysis solution and used cautiously when necessary.
- For further information, specialized references on peritoneal dialysis and the manufacturer's product information (where available) should be consulted.

Haemodialysis Solution

ATC code: B05XA30

Solution, LOU 4

Indications and dose

Adult

Correct electrolyte imbalance and fluid overload and remove metabolites in renal failure: Individualized according to clinical condition and based on blood results

Paediatric

Individualized according to clinical condition and based on blood results.

Contraindications: Shock or severe low blood pressure (systolic pressure <80 mmHg), Pulmonary edema and heart failure due to severe myocardial lesions, Severe arrhythmia, Serious bleeding tendency or brain bleeding, End stage malignant tumor, Extreme failure or dying patients, Patients have mental illness or refuse hemodialysis treatment

Precautions: If patients have one of the contraindications, they had better choose some alternative therapies to dialysis i.e. Adopt conservative therapies (Clear Blood Pollution Therapy or Immunotherapy)

Adverse effects: Low blood pressure is common. You could also have nausea, vomiting, dry or itchy skin, muscle cramps, or feel very tired.

Notes:

- The prevalence of potential drug- Interaction with other medicines among hemodialysis patients is very common, they are highly expected and depend on the number of drugs taken by the patients which were used to treat co-morbid conditions. Many of these interactions are considered as preventable medication related problems, so screening for potential interactions and monitoring regularly should take place routinely before prescribing any medication to improve quality of prescribing and dispending.

25. Medicines For Mental & Behavioural Disorder

25.1. Medicines Used In Psychotic Disorders

Aripiprazole

ATC code: N05AX12

Tablet, 5 mg, 15 mg, LOU 4

Indications and dose

Adult

Schizophrenia, oral: 10-15 mg/day initially; may increase after 2 weeks at each dose strength; not to exceed 30 mg/day when administered as tablet formulation; efficacy not significantly greater above 15 mg/day

Bipolar Mania, oral:

Indicated for acute and maintenance treatment of manic or mixed episodes associated with bipolar I disorder, either as monotherapy or as adjunct to lithium or valproate

- Monotherapy: 15 mg/day initially; may be increased gradually; not to exceed 30 mg/day
- Adjunct to lithium or valproate: 10-15 mg/day initially; recommended daily dose is 15 mg/day; may be gradually increased; not to exceed 30 mg/day
- Continue stabilization dose for up to 6 weeks; treatment >6 weeks not studied

*Major Depressive Disorder, oral:*2-5 mg/day initially; increased weekly as required by ≤5 mg/day to dose range of 2-15 mg/day

Used adjunctively with other antidepressants

Paediatric

Treatment of schizophrenia, oral:

Child<13 years: Safety and efficacy not established

Adolescent 13-17 years: 2 mg/day initially; increase to 5 mg/day after 2 days; may further increase to recommended dose of 10 mg/day after additional 2 days; subsequent doses may increase by 5 mg/day; maintenance: 10-30 mg/day

Indicated for acute manic or mixed episodes, either as monotherapy or as adjunct to lithium or valproate, oral:

Child and adolescent 10-17 years: 2 mg/day initially; increased to 5 mg/day after 2 days; may further increase to recommended dosage of 10 mg/day after additional 2 days; subsequent doses may increase by 5 mg/day; maintenance: 10-30 mg/day

Irritability associated with autistic disorder, oral:

Child <6 years: Safety and efficacy not established

Child 6-17 years: 2 mg/day initially; increase gradually at ≥1 week intervals to target dosage of 5 mg/day; may gradually be further increase as required to 10 mg/day or higher; not to exceed 15 mg/day

Contraindications: Hypersensitivity to aripiprazole, CNS depression, comatose state, phaeochromocytoma

Precautions: Cerebrovascular disease, elderly (reduce initial dose)

Hepatic impairment: Dose adjustment is not necessary.

Renal impairment: Dose adjustment is not necessary.

Pregnancy: Foetal risk cannot be ruled out. Consider risk versus benefit

Breastfeeding: Aripiprazole is present in breast milk. Infant risk cannot be ruled out. Weigh risk versus benefit.

Adverse effects: Common: Weight gain, Headache, Decreased HDL cholesterol, increased LDL cholesterol, increased serum cholesterol, increased serum triglycerides, Akathisia. Less common: Agitation, Insomnia, Anxiety, Nausea and vomiting, Lightheadedness, Constipation, Dizziness, Dyspepsia, Somnolence, Fatigue, Restlessness, Tremor, Dry mouth/xerostomia, Extrapyramidal disorder, Orthostatic hypotension, Musculoskeletal stiffness, Abdominal discomfort, Blurred vision, Cough, Pain, Myalgia, Rash, Rhinitis

Interaction with other medicines (*indicates serious)

*Bromoride, *Cisapride, *Fluconazole, *Ketoconazole, *Metoclopramide, *Piperaquine, Alfusozin, Alprazolam, Amiodarone, Azithromycin, Bedaquiline, Bromazepam, Carbamazepine, Ciprofloxacin, Cetirizine, Phenytoin, Terbinafine

Chlorpromazine

ATC code: N05AA01

Injection, 25 mg (as HCl)/mL in 2-mL amp, LOU 2

Tablet, 50 mg and 100 mg (HCl), LOU 2

Indications and dose

Adult

Schizophrenia, autism, psychomotor agitation and violent behaviour, adjunct in severe anxiety, other psychotic disorders, Oral: Initially 25 mg 3 times daily or 75 mg at night, adjusted according to response to usual maintenance dose of 75–300 mg daily (but up to 1 g daily may be required in psychoses),

- **Elderly** (or debilitated) third to half adult dose
- *For relief of acute symptoms, by deep IM injection:* 25–50 mg every 6–8 hours,

Paediatric

Childhood schizophrenia and autism, oral:

Child 1–12 years: 500 micrograms/kg every 6–8 hours (1–5 years, maximum, 40 mg daily, 6–12 years, maximum, 75 mg daily) (see also Precautions and Adverse effects).

Childhood schizophrenia, autism, severe anxiety and other psychoses, Oral:

Child 1–5 years:500 micrograms/kg every 4–6 hours (maximum 40 mg daily),

Child 6–12 years: third to half adult dose (maximum 75 mg daily).

Relief of acute symptoms of psychoses (including psychomotor agitation and violent behaviour), Deep IM:

Child 1–6 years: 500 micrograms/kg every 6–8 hours (maximum 40 mg daily).

Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour, severe anxiety (adjunct),

Contraindications: Impaired consciousness due to CNS depression, phaeochromocytoma, narrow angle glaucoma, bone marrow suppression, severe liver or cardiac disease, hypersensitivity to chlorpromazine (cross-sensitivity with other phenothiazines may exist), breastfeeding.

Precautions: Cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, renal and hepatic impairment (avoid if severe), history of jaundice, leukopenia (monitor blood counts if unexplained fever or infection), hypothyroidism, myasthenia gravis, prostatic hypertrophy, avoid abrupt withdrawal, patients should remain supine, and the blood pressure monitored for 30 minutes after IM injection.

Skilled Tasks: Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery.

Hepatic impairment: Can precipitate coma, hepatotoxic.

Renal impairment: Start with small doses, increased cerebral sensitivity.

Adverse effects: Sedation, anxiety, agitation, extrapyramidal adverse effects, orthostatic hypotension, tachycardia, blurred vision, mydriasis, constipation, nausea, dry mouth, urinary retention, weight gain, hyperprolactinaemia (may result in galactorrhoea, gynaecomastia, amenorrhoea or infertility), photosensitivity, phototoxicity and hyperpigmentation.

Cholestatic jaundice, allergic reactions (including urticaria, SJS), corneal and lens opacities, SIADH secretion, hyperthermia, hypothermia, neuroleptic malignant syndrome (see below), anaemia, thrombocytopenia, agranulocytosis, venous thromboembolism, eCG changes (reversible, broadened QT interval), arrhythmias, cardiac arrest, sudden death, hepatic fibrosis, priapism, SLE, seizures, increased blood glucose, dysarthria, dysphagia.

Extrapyramidal adverse effects: Dystonias Torticollis, carpopedal spasm, trismus, perioral spasm and oculogyric crisis, as well as medical emergencies, such as laryngeal spasm and opisthotonos, may occur. Dystonias are more common in children and young adults and more likely with high doses. They often occur within 24–48 hours of starting treatment or increasing dose and respond rapidly to anticholinergics. In some cases, treatment with a benzodiazepine may also prove helpful. It may be possible to reintroduce the drug at a lower dose or consider an alternative.

Akathisia: A feeling of motor restlessness, usually occurs 2–3 days (up to several weeks) after starting treatment and may subside spontaneously. It is important to differentiate between akathisia and agitation secondary to psychosis. Akathisia tends to improve with dose reduction and deteriorate when the dose is increased, agitation due to psychosis tends to improve if the dose is increased and deteriorate if it is reduced.

Parkinsonism: Characterized by features such as tremor, rigidity or bradykinesia, usually develops after weeks or months. Although usually reversible, symptomatic treatment is sometimes necessary. Short-term use of an anticholinergic may be helpful. If parkinsonism persists, consider reducing antipsychotic dose or switching to an alternative antipsychotic.

Tardive dyskinesia (TD) Characterized by involuntary movements of the face, mouth or tongue, and sometimes head and neck, trunk or limbs. TD may appear after medium to long-term treatment, or even after stopping the antipsychotic (particularly after suddenly stopping). Up to a third of people treated for 10 years with conventional antipsychotics will develop TD. There may be a slow improvement after the drug is withdrawn, particularly in young patients or early in the syndrome.

Neuroleptic malignant syndrome (NMS) A potentially fatal condition characterized by fever, marked muscle rigidity, altered consciousness and autonomic instability. The syndrome usually progresses rapidly over 24–72 hours. elevation of serum creatine kinase concentration (skeletal muscle origin) and leukocytosis often occur. Not all typical signs need to be present for diagnosis. The incidence of NMS is greatest in young men. It does not always occur immediately after starting antipsychotic treatment, and may be seen after many months or years. Treatment involves ceasing the antipsychotic, general supportive care such as cooling, volume replacement and treatment of hyperkalaemia. Paralysis and mechanical ventilation may also be required.

Metabolic effects People with schizophrenia are at increased cardiovascular risk. Antipsychotic agents have been associated with increased blood glucose, weight gain and dyslipidaemia. Increases risk of type 2 diabetes.

Interaction with other medicines (*indicates serious):

* Amitriptyline: increased risk of antimuscarinic adverse effects, increased plasma amitriptyline concentration, possibly increased risk of ventricular arrhythmias.

Amodiaquine: plasma concentration of chlorpromazine increased (consider reducing chlorpromazine dose).

Antacids (aluminium hydroxide, magnesium hydroxide): reduced absorption of chlorpromazine.

Artemether + lumefantrine: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

Atropine: increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration).

* Carbamazepine: antagonism of anticonvulsant effect (convulsive threshold lowered).

* Clomipramine: increased antimuscarinic adverse effects, increased plasma clomipramine

concentration, possibly increased risk of ventricular arrhythmias. Codeine: enhanced sedative and hypotensive effect.

Diazepam: enhanced sedative effect.

Dopamine: antagonism of hypertensive effect.

Enalapril: enhanced hypotensive effect. Epinephrine: antagonism of hypertensive effect. Ethanol: enhanced sedative effect.

* Ethosuximide: antagonism of anticonvulsant effect (convulsive threshold lowered).

* Erythromycin: increased risk of cardiotoxicity.

* Fluoxetine: increased risk of cardiotoxicity.

Furosemide: enhanced hypotensive effect.

* Halothane: enhanced hypotensive effect.

Hydrochlorothiazide: enhanced hypotensive effect.

* Ketamine: enhanced hypotensive effect.

* Metoclopramide: increased risk of extrapyramidal effects.

Morphine: enhanced sedative and hypotensive effect. Nifedipine: enhanced hypotensive effect.

Nitrous oxide: enhanced hypotensive effect.

* Phenobarbital: antagonism of anticonvulsant effect (convulsive threshold lowered).

* Phenytoin: antagonism of anticonvulsant effect (convulsive threshold lowered).

* Procainamide: increased risk of ventricular arrhythmias.

* Propranolol: concomitant administration may increase plasma concentration of both drugs, enhanced hypotensive effect.

* Ritonavir: plasma concentration possibly increased by ritonavir. Spironolactone: enhanced hypotensive effect.

* Thiopental: enhanced hypotensive effect.

* Valproic acid: antagonism of anticonvulsant effect (convulsive threshold lowered).

Notes:

- Warning: Owing to the risk of contact sensitization, pharmacists, nurses and other health workers should avoid direct contact with chlorpromazine, tablets should not be crushed and solutions should be handled with care.
- Not recommended for rapid tranquillization as locally irritant if given intramuscularly, can alter QTc interval and cause hypotension when given at high dose.
- Deep IM injection is very painful, particularly in children.

Clozapine

ATC code: N05AH02

Tablet (scored), 100 mg, LOU 5

Indications and dose:

Adult

Resistant schizophrenia, Psychosis during the course of Parkinson's disease, Treatment-resistant schizophrenic patients, oral: Starting Therapy: 12.5 mg once or twice on the first day, followed by 25 mg once or twice on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime.

Suicidal behavior in schizophrenia or schizoaffective disorder: Oral: Initial, 12.5 mg once or twice daily, increased, as tolerated, in increments of 25 to 50 mg daily to a target dose of 300 to 450 mg daily (administered in divided doses) by the end of 2 weeks, may further titrate in increments not exceeding 100 mg and no more frequently than once or twice weekly.

Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed, oral: A starting dose of 12.5 mg/day gradually increased over weeks to a maximum of 50 mg/day.

Paediatric

Schizophrenia, treatment resistant, Initial dose, oral:

Child ≥6 years: 6.25 or 12.5 mg once daily

Adolescents: 12.5 mg once or twice daily.

Schizophrenia, treatment resistant, Titration and maintenance dosing, oral: Increase daily dose by ≤25 mg increments (lower initial doses should use smaller increments [1 to 2 times the starting dose]), as tolerated, every 3 to 5 days, to a target dose of 200 to 400 mg/day in divided doses.

Note: Dose should be individualized based on tolerability, concomitant antipsychotic therapy, and clinical response.

Contraindication: Hypersensitivity to the active substance or to any of the excipients. Patients unable to undergo regular blood tests.

History of toxic or idiosyncratic granulocytopenia/ agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).

History of Clozapine-induced agranulocytosis.

Clozapine treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis, concomitant use of depot antipsychotics is to be discouraged

Impaired bone marrow function, Uncontrolled epilepsy, Alcoholic and other toxic psychoses, drug intoxication, comatose conditions. Circulatory collapse and/or CNS depression of any cause, Severe renal or cardiac disorders (e.g., myocarditis).

Active liver disease associated with nausea, anorexia

or jaundice, progressive liver disease, hepatic failure, Paralytic ileus.

Hepatic impairment: Dose adjustment may be necessary in significant impairment.

Renal impairment: Dose adjustment may be necessary in significant impairment

Pregnancy: Clozapine crosses the placenta. Foetal risk cannot be ruled out.

Breastfeeding: Clozapine is present in breast milk. Its use is not recommended in breastfeeding women.

Adverse effects: Common: seizure, cardiovascular effects, fever, drowsiness/sedation, dizziness, tachycardia, constipation and hyper salivation, dyspepsia, nausea, vomiting, hypercholosteremia, hypertriglyceridemia, weight gain, hyperglycemia Less common: agranulocytosis, diarrhoea, heartburn, visual disturbance, diaphoresis, syncope

Interaction with other medicines (*indicates serious)

*Amiodarone, barbiturates, *benzodiazepines, *Carbamazepine, *carbegoline, chloramphenicol, sulphonamides (e.g., co-trimoxazole), pyrazolone analgesics (e.g., phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics

Flupentixol

ATC code: N05AF01

Injection (oily depot), 20 mg/mL as decanoate (2-mL amp), LOU 4

Indications and dose:

Adult

Primary and secondary symptoms of psychotic disorders, Patients with prior exposure and good tolerance of long-acting depot antipsychotics, IM: 20 to 40 mg. Maintenance: 20 to 40 mg may be given 4 to 10 days after initial injection (if well tolerated), followed by usual maintenance dose of 20 to 40 mg every 2 to 3 weeks.

Dose is individualized and titrated in maximum increments of ≤20 mg (doses >80 mg are not usually necessary.). Dose should be maintained at the lowest effective dose.

Paediatric: Contraindicated

Contraindication: Children, CNS depression, comatose states, excitable patients, overactive patients

Hepatic impairment: Dose adjustment not necessary. Use caution

Renal impairment: Dose adjustment not necessary.

Pregnancy: Use in third trimester increases the risk of abnormal muscle movement and withdrawal effects.

Breastfeeding: Adverse effects are unlikely in nursing infants.

Adverse effects: akathisia, extrapyramidal effects, tardive dyskinesia, dystonic reactions

Interaction with other medicines (* indicates serious):

Alcohol, amphetamines, anticholinergics, antihistamines, anticonvulsants, *metoclopramide, Nitroglycerine*potassium chloride, *thalidomide, *tiotropium, *zolpidem

Note:

» Initiate with oral therapy, upon stabilization, patients may then be transitioned to the depot injection.

Fluphenazine

ATC code: N05AB02

Injection, (oily depot): 25 mg/1-mL amp as decanoate, LOU 4

Indications and dose

Adult

Treatment and maintenance of schizophrenic patients and those with paranoid psychoses, 0.5 mL (12.5 mg) to 4.0 mL (100 mg) given at a dose interval of 2 to 5 weeks.

Paediatric: Contraindicated

Contraindication: children, confusional states, impaired consciousness due to CNS depression, parkinsonism, intolerance to antipsychotics, depression, bone marrow depression, phaeochromocytoma, marked cerebral artherosclerosis.

Precautions: The dosage should not be increased without close supervision and it should be noted that there is variability in individual response.

Hepatic impairment: Contraindicated

Renal impairment: Dose adjustment not necessary. Use with caution

Pregnancy: Antipsychotic use during the third trimester of pregnancy has a risk for abnormal muscle movements (extrapyramidal symptoms [EPS]) and withdrawal symptoms in newborns following delivery.

Breastfeeding: Avoid breastfeeding if possible. Monitor infant for Adverse effects

Adverse effects: drowsiness, lethargy, blurred vision, dryness of the mouth, constipation, urinary hesitancy or incontinence, mild hypotension, impairment of judgement and mental skills, and epileptiform attacks.

Interaction with other medicines (*indicates serious):

*Bromopride, *Dronedarone, *Metoclopramide, *Saquinavir, Alprazolam, Bromazepam, codeine, Doxorubicin, Epinephrine, Gabapentin, Ketamine, Lithium, Methadone, Morphine, Tramadol

Note:

» Prior to initiation consider establishing response, the appropriate dose and tolerability with a short-acting form of fluphenazine.

Haloperidol

ATC code: N05AD01

Injection, 5 mg in 1-mL amp, LOU 4

Injection (oily), 50 mg/mL, amp, LOU 4

Tablet (scored), 5 mg, LOU 2

Indications and Dose:

Adult

Schizophrenia and other psychoses, mania, short-term adjunctive management of psychomotor agitation, violent behaviour, and severe anxiety, oral:

Moderate disease: 0.5 to 2mg every 8 to 12 hours initially

Severe disease: 3 to 5mg every 8 to 12 hours initially; not to exceed 30mg per day

(half of the adult dose in elderly or debilitated patients, 3–5 mg 2–3 times daily in severely affected or resistant patients, up to 30 mg daily in resistant schizophrenia),

Schizophrenia, Psychosis, IM (immediate acting – lactate): 2 – 5 mg every 4 to 8 hours as required; May require every one hour in acute agitation; not to exceed 20 mg per day

Schizophrenia, Psychosis, IM depot (decanoate):

Initial dose: IM dose 10 – 20 times daily oral dose administered monthly; not to exceed 100mg; if conversion requires initial dose greater than 100mg, administer in 2 injections (e.g. 100mg initially, then remainder in 3 to 7 days)

Maintenance: Monthly dose 10 – 15 times daily oral dose.

Paediatric

Schizophrenia, psychosis/sedation, oral:

Child < 3years: safety and efficacy not established

Child 3–12 years (15 – 40kg): initially 0.125–0.25 mg twice daily, increase by 0.25–0.5 mg/day every 5–7 days as required. Maximum 0.15 mg/kg daily. Usual maintenance 0.025–0.05 mg/kg three times daily. IM (when rapid effect required).

Schizophrenia, psychosis/sedation, IM lactate (immediate acting):

Child 6–12 years: 1–3 mg per dose every 4–8 hours to a maximum of 0.15 mg/kg daily. Change to oral therapy as soon as possible.

Behavioral Disorders, oral:

Child<3 years: Safety and efficacy not established

Child 3-12 years: 0.5 mg/day initially; dose increased as required by 0.5 mg every 5-7 days until therapeutic effect achieved, then reduced to lowest effective maintenance level of 0.05-0.075 mg/kg/day divided q8-12hr

Acute Agitation, oral:

Child<12 years: Safety and efficacy not established

Child >12 years: 0.5-3 mg, repeated in 1 hour as required; alternatively, 2-5 mg IM, repeated in 1 hr as required

IM depot decanoate not recommended in children

Contraindications: Impaired consciousness due to CNS depression, bone marrow depression, phaeochromocytoma, porphyria, basal ganglia disease, severe liver or cardiac disease.

Precautions: Cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, renal and hepatic impairment (avoid if severe), history of jaundice, leukopenia (blood count required if unexplained fever or infection), hypothyroidism, myasthenia gravis, prostatic hypertrophy, closed-angle glaucoma, subarachnoid haemorrhage, metabolic disturbances such as hypokalaemia, hypocalcaemia or hypomagnesaemia, avoid abrupt withdrawal, patients should remain supine and have their blood pressure monitored for 30 minutes after IM injection.

Skilled Tasks: Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery.

Hepatic impairment: Can precipitate coma, consider dose reduction. Avoid use in severe impairment.

Renal impairment: Severe: start with small doses, increased cerebral sensitivity.

Adverse effects: Sedation, anxiety, agitation, extrapyramidal adverse effects, orthostatic hypotension, tachycardia, blurred vision, mydriasis, constipation, nausea, dry mouth, urinary retention, weight gain, hyperprolactinaemia (may result in galactorrhoea, gynaecomastia, amenorrhoea or infertility).

or rare Allergic reactions, including urticaria, SJS, corneal and lens opacities, SIADH, hyperthermia, hypothermia, neuroleptic malignant syndrome (see below), anaemia, thrombocytopenia, agranulocytosis, venous thromboembolism, eCG changes (reversible, broadened QT interval), arrhythmias, cardiac arrest, sudden death, hepatic fibrosis, priapism, SLE, seizures, increased blood glucose (see Metabolic effects below), dysarthria, dysphagia, weight loss, hypoglycaemia.

Dystonias: Torticollis, carpopedal spasm, trismus, perioral spasm and oculogyric crisis, as well as medical emergencies, such as laryngeal spasm and opisthotonos, may occur. Dystonias are more common in children and young adults, and more likely with high doses. They often occur within 24–48 hours of starting treatment or increasing dose, and respond rapidly to anticholinergics. In some cases, treatment with a benzodiazepine may also prove helpful. It may be possible to reintroduce the drug at a lower dose, or consider an alternative.

Akathisia: A feeling of motor restlessness, usually occurs 2–3 days (up to several weeks) after starting treatment and may subside spontaneously. It is important to differentiate between akathisia and agitation secondary to psychosis. Akathisia tends to improve with dose reduction and deteriorate when the dose is increased, agitation due to psychosis tends to improve if the dose is increased and deteriorate if it is reduced. Children may not complain of the sensation of akathisia in the same way as adults, monitor closely. Sedating agents such as haloperidol are more likely to impair cognition and therefore learning at school.

Parkinsonism: Characterized by features such as tremor, rigidity or bradykinesia, usually develops after weeks or months. Although usually reversible, symptomatic treatment is sometimes necessary. Short-term use of an anticholinergic may be helpful. If parkinsonism persists, consider reducing antipsychotic dose or switching to an alternative antipsychotic (possibly an atypical agent).

Tardive dyskinesia (TD) Characterized by involuntary movements of the face, mouth or tongue, and sometimes head and neck, trunk or limbs. TD may appear after medium to long-term treatment, or even after stopping

the antipsychotic (particularly after suddenly

stopping). Diabetics and those with affective disorders appear to

be at increased risk. Up to a third of people treated for 10 years with conventional antipsychotics will develop TD. There may be a slow improvement after the drug is withdrawn, particularly in young patients or early in the syndrome.

Neuroleptic Malignant Syndrome (NMS) All antipsychotics can cause NMS, a potentially fatal condition characterized by fever, marked muscle rigidity, altered consciousness and autonomic instability. The syndrome usually progresses rapidly over 24–72 hours. elevation of serum creatine kinase concentration (skeletal muscle origin) and leukocytosis often occur. Not all typical signs need to be present for diagnosis. The incidence of NMS is greatest in young men. It does not always occur immediately after starting antipsychotic treatment, and may be seen after many months or years. Treatment involves ceasing the antipsychotic, general supportive care such as cooling, volume replacement and treatment of hyperkalaemia. Paralysis and mechanical ventilation may also be required.

Metabolic effects People with schizophrenia are at increased cardiovascular risk. Antipsychotic agents have been associated with increased blood glucose, weight gain, dyslipidaemia and an increased risk of type 2 diabetes.

Interaction with other medicines (*indicates serious):

* Amitriptyline: increased plasma amitriptyline concentration, possibly increased risk of ventricular arrhythmias.

* Artemether + lumefantrine: manufacturer of artemether with lumefantrine advises avoidance of concomitant use.

Atropine: possible reduced effects of haloperidol.

* Carbamazepine: antagonism of anticonvulsant effect (convulsive threshold lowered), metabolism of haloperidol accelerated (reduced plasma concentration).

* Clomipramine: increased plasma clomipramine concentration, possible increased risk of ventricular arrhythmias.

Codeine: enhanced sedative and hypotensive effect. Diazepam: enhanced sedative effect.

Dopamine: antagonism of hypertensive effect. Enalapril: enhanced hypotensive effect. Epinephrine: antagonism of hypertensive effect.

* Erythromycin: increased risk of cardiotoxicity. Ethanol: enhanced sedative effect.

* Ethosuximide: antagonism of anticonvulsant effect (convulsive threshold lowered).

Fluoxetine: plasma concentration of haloperidol increased.

* Halothane: enhanced hypotensive effect.

* Ketamine: enhanced hypotensive effect.

* Metoclopramide: increased risk of extrapyramidal effects.

Morphine: enhanced sedative and hypotensive effect.

Nifedipine: enhanced hypotensive effect.

* Nitrous oxide: enhanced hypotensive effect.

* Phenobarbital: antagonism of anticonvulsant effect (convulsive threshold lowered), metabolism of haloperidol accelerated (reduced plasma concentration).

* Phenytoin: antagonism of anticonvulsant effect (convulsive threshold lowered).

* Procainamide: increased risk of ventricular arrhythmias.

* Quinidine: increased risk of ventricular arrhythmias.

* Rifampicin: accelerated metabolism of haloperidol (reduced plasma haloperidol concentration).

* Ritonavir: plasma concentration possibly increased by ritonavir.

* Thiopental: enhanced hypotensive effect.

* Valproic acid: antagonism of anticonvulsant effect (convulsive threshold lowered).

Midazolam

ATC code: N05CD08

Injection, 5 mg/mL (3-mL amp), LOU 4

Indications and dose

Adult

Anxiety and severe agitation, IV, IM: Initial - 2.5 to 5 mg, repeat doses may be administered every 3 to 5 minutes (IV route) or every 5 to 10 minutes (IM route) until sedation is adequate and appropriate, some patients may require a total dose of ~20 mg, monitor respiratory status, may give alone or in combination with an antipsychotic.

Paediatric

For all indications in a palliative care setting, SC or IV injection:

Child all ages: 0.05–0.15 mg/kg every 1–2 hours.

For all indications in a palliative care setting, Continuous SC or IV infusion:

Child all ages: 10 micrograms/kg/hour by continuous SC or IV infusion, initially, and titrate to effect.

There is considerable variability in the dose required.

For all indications in a palliative care setting, Oral:

Child all ages: 0.3–0.5 mg/kg (maximum 15 mg) as a single dose. Use the parenteral form, bitter taste can be disguised in apple juice or chocolate sauce.

For all indications in a palliative care setting, Buccal or intranasal:

Child all ages: 0.2–0.5 mg/kg per dose (maximum 10 mg) as required. Use the parenteral form.

Contraindications: Consider the relevance of these listed contraindications in palliative care. Acute or severe pulmonary insufficiency, sleep apnoea syndrome, severe liver disease, myasthenia gravis.

Hepatic impairment: CNS adverse effects increased, avoid in severe impairment as can precipitate coma.

Renal impairment: Mild to moderate impairment: no

dosage reduction necessary.

Severe impairment: use sparingly and titrate according to response. Bolus doses preferred.

Patients with renal impairment may be more susceptible to CNS adverse effects.

Adverse effects: Hypotension, hiccup, cough, apnoea or respiratory depression (particularly with IV administration).

erythema, rash, confusion.

Arrhythmias, cardiorespiratory arrest, anaphylactic reactions.

Interaction with other medicines (*indicates serious):

Atazanavir: inhibits metabolism, prolonging sedation and respiratory depressant effects.

Carbamazepine: may increase midazolam's metabolism and decrease its effect.

Erythromycin: inhibits metabolism and prolongs sedation and respiratory depressant effects.

Fluconazole: inhibits the metabolism of midazolam, prolonging its sedative and respiratory depressant effects.

Lopinavir: inhibits metabolism, prolonging sedation and respiratory depressant effects. Phenytoin: may increase metabolism, decreasing therapeutic effects.

Rifampicin: increases metabolism, decreasing therapeutic effects.

Ritonavir: inhibits metabolism, prolonging sedation and respiratory depressant effects. Saquinavir: inhibits metabolism, prolonging sedation and respiratory depressant effects.

Notes:

- Midazolam injection can be administered orally, buccally or intranasally.
- Onset of action: SC 5–10 minutes, oral 60 minutes, buccal within 15 minutes. Compatible with most drugs commonly administered via syringe driver.

Olanzapine

ATC code: N05AH03

Powder for injection, 10-mg vial, LOU 5

Tablet (dispersible), 10 mg, LOU 3

Tablet, 5 mg, 10 mg, LOU 3

Indications and dose

Adult

Schizophrenia (Combination therapy for mania), oral: 10 mg daily, adjusted according to response, usual dose 5–20 mg daily

Preventing recurrence in bipolar disorder, oral: 10 mg daily, adjusted according to response, usual dose 5–20 mg daily

Monotherapy for mania, oral: 15 mg daily, adjusted according to response, usual dose 5–20 mg daily

Control of agitation and disturbed behaviour in schizophrenia or mania, By IM injection: Initially 5–10 mg for 1 dose, usual dose 10 mg for 1 dose, followed by 5–10 mg after 2 hours if required, maximum 3 injections daily for 3 days, maximum daily combined oral and parenteral dose 20 mg

Paediatric

Schizophrenia, Combination therapy for mania, oral:

Child 12–17 years (under expert supervision): Initially 5–10 mg daily, adjusted according to response, usual dose 5–20 mg daily.

Monotherapy for mania, oral:

Child 12–17 years (under expert supervision): 15 mg daily, adjusted according to response, usual dose 5–20 mg daily,

Contraindication: narrow-angle glaucoma.

Hepatic impairment: Dose adjustment is not necessary except when used in combination with fluoxetine, the initial olanzapine dose should be limited to 2.5 to 5 mg daily

Renal impairment: Dose adjustment is not necessary

Pregnancy: Foetal risk cannot be ruled out.

Breastfeeding: Olanzapine is present in breast milk. Infant risk cannot be ruled out.

Adverse effects: weight gain, somnolence, orthostatic hypotension, rash, erectile dysfunction, anemia, constipation, xerostomia, hypercholesterolaemia, hyperglycaemia, Akathisia, dizziness, personality disorder. Less common: neutropenia, sudden cardiac death, diabetes mellitus

Interaction with other medicines (*indicates serious): carbamazepine, activated charcoal, antiparkinsonian medicines, *saquinavir, *terfenadine, *metoclopramide, *piperaquine

Paliperidone Palmitate

ATC code: N05AX13

Injection, 75 mg/mL, 100 mg/mL, 150 mg/mL, LOU 5

Indications and dose

Adult

Maintenance in schizophrenia in patients previously responsive to paliperidone or risperidone, By deep IM injection: 150 mg for 1 dose on day 1, then 100 mg for 1 dose on day 8, to be injected into the deltoid muscle, dose subsequently adjusted at monthly intervals according to response, maintenance 75 mg once a month.

Maintenance of schizophrenia in patients who are clinically stable on once-monthly IM paliperidone, By deep IM injection: Initially 175–525 mg every 3 months, adjusted according to response, to be administered into the deltoid or gluteal muscle.

Paediatric: Not indicated in children.

Contraindication: Documented hypersensitivity to paliperidone or risperidone

Precautions: Cataract surgery (risk of intraoperative floppy iris syndrome), dementia with Lewy bodies, elderly patients with dementia, elderly patients with risk factors for stroke, predisposition to gastro-intestinal obstruction, prolactin-dependent tumours.

Hepatic impairment: No dose adjustment necessary. Use caution in severe impairment.

Renal impairment: Adjust dose in CrCl 50–79 mL/min. Avoid if CrCl <50 mL/min.

Pregnancy: Foetal risk cannot be ruled out. Use only if potential benefits outweigh risks.

Breastfeeding: Present in breast milk. Avoid.

Adverse effects: Common: Akathisia, Somnolence, Insomnia, Parkinsonism, Tachycardia, Hyperprolactinemia, Cough, Dystonia, Extrapyramidal symptoms (EPS), Orthostatic hypotension, nasopharyngitis, weight gain, constipation Less common: QT prolongation, Sialorrhea, Priapism, Indigestion, Amenorrhea, Galactorrhea, Nausea, Dyspepsia, Salivation, Xerostomia, Myalgia, Extremity pain, Angioedema, swollen tongue, Ileus, Thrombotic thrombocytopenic purpura, Urinary incontinence, urinary retention, Falls

Interaction with other medicines (*indicates serious): *cisapride, *metoclopramide, *piperaquine, *saquinavir, *azelastine, *blonanserin, *buprenorphine, *cabergoline, haloperidol, lithium, oxycodone, *thalidomide

Quetiapine

ATC code: N05AH04

Tablet (i/r, scored), 100 mg, 200 mg, 300 mg, LOU 4

Tablet (e/r), 200 mg, 300 mg, LOU 4

Indications and dose

Adult

Schizophrenia and moderate to severe manic episodes in bipolar disorder, oral: 400–800 mg daily, depending on the clinical response and tolerability by the patient.

Major depressive episodes in bipolar disorder, oral: 50 mg (day 1), 100 mg (day 2), 200 mg (day 3) and 300 mg (day 4).

Paediatric

Bipolar I disorder, acute management, monotherapy, oral:

Child 10–17 years: 25 mg twice daily on day 1, 100 mg divided twice daily on day 2, 200 mg divided twice daily on day 3, 300 mg divided twice daily on day 4, 400 mg divided twice daily on day 5 with further dose adjustments with increments of not more than 100 mg/day up to a maximum of 600 mg/day.

Schizophrenia, oral:

Child 13–17 years: 25 mg twice daily on day 1, 100 mg divided twice daily on day 2, 200 mg divided twice daily on day 3, 300 mg divided twice daily on day 4, 400 mg divided twice daily on day 5 with further dose adjustments with increments of not more than 100 mg/day up to a maximum of 800 mg/day.

Contraindication:

Hypersensitivity to quetiapine or any component of the product

Precautions:

Cerebrovascular disease, elderly, patients at risk of aspiration pneumonia, treatment of depression in patients under 25 years (increased risk of suicide)

Hepatic impairment: Initial: 25 mg once daily, increase dose by 25 to 50 mg/day to effective dose, based on individual clinical response and tolerability.

Renal impairment: Dose adjustment is not necessary.

Pregnancy: Use only if potential benefit outweighs risk. Foetal risk cannot be ruled out.

Breastfeeding: Quetiapine is present in breast milk.

Adverse effects: Common: somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation), symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

Less common: Seizures, suicidal thoughts, tardive dyskinesia, syncope, sudden cardiac death.

Interaction with other medicines (*indicates serious): Alcohol, *azelastine, *cabergoline, *carbamazepine, *clozapine, haloperidol, lithium, *metoclopramide, ketoconazole, phenytoin, antidiabetic agents, ondansetron.

Risperidone

ATC code: N05AX08

Tablet (scored), 2 mg, LOU 3

Indications and dose

Adult

Acute and chronic psychosis, oral: 2 mg daily in 1–2 divided doses for day 1, then 4 mg daily in 1–2 divided doses for day 2, slower titration is appropriate in some patients, usual dose 4–6 mg daily.

Mania, oral: Initially 2 mg once daily, then increased in steps of 1 mg daily if required, usual dose 1–6 mg daily

Paediatric

Autism associated irritability including aggression, temper, tantrums, self injurious behavior and quickly changing moods, oral:

Child 5 to 8 years: 15 to 20 kg: Initial 0.25 mg once daily after≥4 days may increase dose to 0.5 mg/day, maintain this dose for ≥14 days. In patients not achieving clinical response, may increase dose in increments of 0.25 mg/day at ≥2 week intervals.

≥20 kg: Initial:0.5 mg once daily after ≥4 days may increase dose to 1 mg/day, maintain this dose for ≥14 days. In patients not achieving clinical response, may increase dose in increments of 0.5 mg/day at ≥2 week intervals.

Bipolar Mania, oral:

Children and adolescents 10 to 17 years: Initial:0.5 mg once daily, Dose adjusted if needed in increments of 0.5 mg/day to 1 mg/day at intervals ≥24hours as tolerated, to a dose of 2.5 mg/day.

Contraindication:

hypersensitivity to risperidone.

Precautions: Avoid in Acute porphyria, cataract surgery (risk of intra-operative floppy iris syndrome), dehydration, dementia with Lewy bodies, prolactin-dependent tumours

Use in pregnancy/breastfeeding, limited data. Weigh the benefits against the risks.

Hepatic impairment: severe impairment (Child-Pugh

class C): Initial: 0.5 mg twice daily, titration should progress slowly in increments of no more than 0.5 mg twice daily, increases to dosages >1.5 mg twice daily should occur at intervals of ≥1 week.

Renal impairment: Severe impairment (CrCl <30 mL/min): Initial: 0.5 mg twice daily, titrate slowly in increments of no more than 0.5 mg twice daily, increases to dosages >1.5 mg twice daily should occur at intervals of ≥1 week.

Pregnancy: Use only if potential benefits outweigh risks.

Breastfeeding: Risperidone is present in breast milk. Consider risk to infant versus benefits of breastfeeding and benefits of treating the mother.

Adverse effects: Insomnia, sedation/somnolence, Parkinsonism, headache, tachycardia, blurred vision, weight gain, infections, hypertension, rash.

Interaction with other medicines: Alcohol, levodopa, carbamazepine, Tricyclic antidepressants, ketoconazole

Zuclopenthixol

ATC code: N05AF05

Injection (aqua), 100mg/mL (2mL amp as acetate), LOU 4

Injection (oily, depot), 200 mg/1 mL as decanoate in amp, LOU 4

Oral drops, 20 mg/mL (20 mL), LOU 4

Indications and dose:

Adult

Zuclopenthixol acetate

Initial treatment of acute psychoses including mania and exacerbation of chronic psychoses, particularly where duration of effect of 2–3 days is desirable, deep IM into the upper outer buttock or lateral thigh (injection volumes exceeding 2ml should be distributed between two injection sites: 50–150 mg (1–3 mL), repeated if necessary after 2 or 3 days

Some patients may need an additional injection between 1 and 2 days after the first injection. No more than 400 mg or 4 injections should be given in the course of treatment. Duration of treatment not to exceed 2 weeks.

Zuclopenthixol decanoate

*Long term management of psychosis, deep IM into upper outer buttock or lateral thigh:*200 to 500mg every one to four weeks depending on response; Some patients require up to 600mg per week. The maximum single dose at any one time is 600mg.

Treatment is started with a low dose of 100mg and increased at an interval of at least 1 week.

Transfer of patients from IM acetate to IM decanoate:

Note: When initiating maintenance therapy with decanoate, may administer initial dose concomitantly with final acetate injection:

50 mg of acetate injection every 2 to 3 days = 100 mg of decanoate injection every 2 weeks

100 mg of acetate injection every 2 to 3 days = 200 mg of decanoate injection every 2 weeks

150 mg of acetate injection every 2 to 3 days = 300 mg of decanoate injection every 2 weeks

Acute schizophrenia and other acute psychoses. Severe acute states of agitation. Mania, Oral: Usually 10–50 mg/day, increased if necessary by 10 (to 20) mg every 2 to 3 days up until 100–150 mg divided in 2–3 doses per day.

Chronic schizophrenia and other chronic psychoses, oral: Maintenance dosage usually 20–40 mg/day.

Agitation in mentally retarded patients, oral: 6–20 mg/day, if necessary increased to 25–40 mg/day.

» Older patients should receive dosages in the lower end of the dosage range.

Paediatric: Not indicated for use in children due to lack of clinical experience

Contraindication: Apathetic states, CNS depression, comatose states, phaeochromocytoma, withdrawn states

Precautions: Zuclopenthixol acetate is not intended for long-term use and duration of treatment should not be more than two weeks. The maximum accumulated dosage should not exceed 400 mg and the number of injections should not exceed four.

Hyperthyroidism, hypothyroidism.

Hepatic impairment: Dose adjustment not necessary. Use with caution in hepatic impairment.

Renal impairment: Dose adjustment not necessary. Start with small doses in severe renal impairment because of increased cerebral sensitivity.

Pregnancy: Antipsychotic use during the third trimester of pregnancy has a risk for abnormal muscle movements (extrapyramidal symptoms [EPS]) and withdrawal symptoms in newborns following delivery. Symptoms in the newborn may include agitation, feeding disorder, hypertonia, hypotonia, respiratory distress, somnolence, and tremor, these effects may be self-limiting or require hospitalization.

Adverse effects: Thrombocytopenia, neutropenia, leukopenia, agranulocytosis, Hypersensitivity, anaphylactic reaction, Insomnia, depression, anxiety, nervousness, abnormal dreams, agitation, libido decreased, Somnolence, akathisia, hyperkinesia, hypokinesia

Interaction with other medicines:

zuclopenthixol enhances the response to alcohol, the effects of barbiturates and other CNS depressants.

Zuclopenthixol may potentiate the effects of general anaesthetics and anticoagulants and prolong the action of neuromuscular blocking agents.

The anticholinergic effects of atropine or other drugs with anticholinergic properties may be increased.

Concomitant use of drugs such as metoclopramide, piperazine or antiparkinson drugs may increase the risk of extrapyramidal effects such as tardive dyskinesia. Combined use of antipsychotics and lithium or sibutramine has been associated with an increased risk of neurotoxicity.

Antipsychotics may enhance the cardiac depressant effects of quinidine, the absorption of corticosteroids and digoxin.

The hypotensive effect of vasodilator antihypertensive agents such as hydralazine and a blockers (e.g., doxazosin), or methyl-dopa may be enhanced.

25.2. Medicines Used In Mood Disorders

25.2.1. Medicines Used In Depressive Disorders

Amitriptyline

ATC code: N06AA09

Tablet, 25 mg, LOU 2

Indications and dose

Adult

Depression (moderate to severe), oral: Initially 75 mg daily in divided doses or as a single dose at bedtime, increased gradually to 150–200 mg daily as necessary

» Elderly: 30–75 mg, daily in the elderly

Paediatric

Depression, Oral:

Child 9 to 12 years: Initial 1 mg/kg/day in 3 divided doses; after 3 days, dose may be increased to 1.5 mg/kg/day in 3 divided doses

Child ≥12 years and adolescents:10 mg three times daily and 20 mg at bedtime; in general, lower doses are recommended compared to adults; maximum daily dose: 200 mg/day

Contraindications: Recent MI, arrhythmias (especially heart block), manic phase

in bipolar disorders, severe liver disease, porphyria.

Precautions: History of epilepsy, hepatic impairment, thyroid disease, phaeochromocytoma, history of mania, psychoses or depression (may aggravate psychotic or depressive symptoms), angle closure glaucoma, history of urinary retention, concurrent electroconvulsive therapy, avoid abrupt withdrawal, anaesthesia (increased risk of arrhythmias and hypotension). Cardiac disease, history of epilepsy, pregnancy and breastfeeding, the elderly (reduce dose), hepatic impairment, thyroid disease, phaeochromocytoma, history of mania or psychoses (may aggravate psychotic symptoms)

Skilled tasks**:** Warn patient or caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours. May impair ability to perform skilled tasks, for example operating machinery or driving.

Hepatic impairment: Sedative effects increased (avoid in severe liver disease}.

Renal impairment: Dose reduction not necessary.

Pregnancy: Foetal risk cannot be ruled out. Use only if potential benefits outweigh risks.

Breastfeeding: Amount secreted in breastmilk is too small to be harmful.

Adverse effects: Common: Sedation, dry mouth, blurred vision (disturbance of accommodation, increased intraocular pressure), constipation, nausea, difficulty in micturition, cardiovascular adverse effects particularly with high dosage including eCG changes, arrhythmias, postural hypotension, tachycardia, syncope, sweating, tremor, rash and hypersensitivity reactions (urticaria, photosensitivity).

Behavioural disturbances, hypomania or mania, confusion or delirium, headache, interference with sexual function, blood sugar changes, increased appetite and weight gain (occasional weight loss), endocrine adverse effects such as testicular enlargement, gynaecomastia and galactorrhoea, movement disorders and dyskinesias, dysarthria, paraesthesia, taste disturbances, tinnitus, fever, abnormal liver function tests.

Rare Blood dyscrasias including agranulocytosis, leukopenia, eosinophilia, purpura and thrombocytopenia, hepatitis, paralytic ileus, SIADH with hyponatraemia, seizures, prolonged QT interval.

In overdose (high rate of fatality), excitement, restlessness, marked anticholinergic effects, severe symptoms including unconsciousness, convulsions, myoclonus, hyper-reflexia, hypotension, acidosis, respiratory and cardiac depression with arrhythmias.

Interaction with other medicines (*indicates serious):

* Alcohol: enhanced sedative effect.

* Atemether + lumefantrine: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

Atropine: increased antimuscarinic adverse effects.

* Carbamazepine: antagonism of anticonvulsant effect (convulsive threshold lowered), accelerated metabolism of amitriptyline (reduced plasma concentration, reduced antidepressant effect).

Chlorpheniramine: increased antimuscarinic and sedative effects.

* Chlorpromazine: increased risk of antimuscarinic adverse effects, increased plasma amitriptyline concentration, possibly increased risk of ventricular arrhythmias. Codeine: possibly increased sedation.

Contraceptives, oral: antagonism of antidepressant effect by estrogens but adverse effects of amitriptyline possibly increased due to increased plasma concentration of amitriptyline.

Diazepam: enhanced sedative effect.

* Epinephrine: increased risk of hypertension and arrhythmias (but local anaesthetics with epinephrine appear to be safe).

* Ethosuximide: antagonism of anticonvulsant effect (convulsive threshold lowered).

* Fluphenazine: increased risk of antimuscarinic adverse effects, increased plasma amitriptyline concentration, possibly increased risk of ventricular arrhythmias.

Furosemide: increased risk of postural hypotension.

Haloperidol: increased amitriptyline concentration, possibly increased risk of ventricular arrhythmias. Halothane: increased risk of arrhythmias and hypotension.

Hydrochlorothiazide: increased risk of postural hypotension.

Isoniazid: increased plasma concentration of isoniazid.

Ketamine: increased risk of arrhythmias and hypotension.

Levothyroxine: enhanced effects of amitriptyline.

Morphine: possibly increased sedation.

Nitrous oxide: increased risk of arrhythmias and hypotension.

* Phenobarbital: antagonism of anticonvulsant effect (convulsive threshold lowered), metabolism of amitriptyline possibly accelerated (reduced plasma concentration).

* Phenytoin: antagonism of anticonvulsant effect (convulsive threshold lowered), possibly reduced plasma amitriptyline concentration.

Rifampicin: plasma concentration of amitriptyline possibly reduced.

* Ritonavir: plasma concentration possibly increased by ritonavir.

Spironolactone: increased risk of postural hypotension.

Thiopental: increased risk of arrhythmias and hypotension.

* Valproic acid: antagonism of anticonvulsant effect (convulsive threshold lowered).

* Warfarin: enhanced or reduced anticoagulant effect.

Note:

» Amitriptyline is a representative tricyclic antidepressant. Various medicines can serve as alternatives.

Escitalopram

ATC code: N06AB10

Tablet,10 mg, LOU 3

Indications and dose

Adult

Major Depressive Disorder Indicated for acute and maintenance treatment of major depressive disorder, oral: 10 mg day, may increase to 20 mg/day after 1 week

Generalized Anxiety Disorder Indicated for acute treatment of generalized anxiety disorder, oral: 10 mg day, may increase to 20 mg/day after 1 week, maintain at lowest effective dose and assess need of therapy periodically if extended therapy required

Secondary to Depression. oral: 5–20 mg over 8 week period

Secondary to panic disorder in women, oral: 5–10 mg over 8 week period

Paediatric

Depression, oral:

Children and Adolescents ≥12 years: Initial: 10 mg once daily, may be increased to 20 mg/day after at least 3 weeks.

Autism and Pervasive Developmental Disorders, oral:

Children and Adolescents 6 to 17 years: Initial: 2.5 mg once daily, may increase if needed to 5 mg/day after 1 week, may then increase at weekly intervals by 5 mg/day if needed and as tolerated, maximum dose: 20 mg/day.

Social anxiety disorder, oral:

Children and Adolescents 10–17 years: Initial – 5 mg once daily for 7 days, then 10 mg/day for 7 days, may then increase at weekly intervals of 5 mg/day if needed based on clinical response and tolerability, maximum dose: 20 mg/day.

Contraindication: Hypersensitivity to escitalopram or citalopram and Pimozide

MAOIs: Use of MAOIs intended to treat psychiatric disorders with escitalopram or within 14 days of discontinuation, Use of escitalopram within 14 days of stopping an MAOI intended to treat psychiatric disorders, Starting escitalopram in a patients being treated with MAOIs such as linezolid or IV methylene blue

Precautions: previous seizure disorder, monitor worsening of depression or suicidality.

Adverse effects: Headache, Nausea, Ejaculation disorder, Somnolence, Insomnia, Xerostomia, Constipation, Fatigue, Diarrhea, Libido decrease, Anorgasmia, Indigestion, Rhinitis, Flu-like syndrome, Neck/shoulder pain, Decreased appetite, Vomiting, Sinusitis, Lethargy, Menstrual disorder, Flatulence, Toothache, Yawning, Menstrual disorder, Weight gain

Interaction with other medicines (*indicates serious):

*Bromopride, *Cisapride, *Fluconazole, *Linezolid, *Metoclopramide, Aceclofenac

Amiodarone, Amitriptyline, Aripiprazole, Atazanavir, Azithromycin, Bedaquiline, Ciprofloxacine, codeine, Diclofenac, Etodolac, Etofenamate, Etoricoxib, Flufenamic acid, Ibuprofen, Indomethacin, Ketorolac

Fluoxetine

ATC code: N06AB03.

Tablet (scored), 20 mg (as HCl), LOU 3

Indications and dose

Adult

Major depression, oral: Initially 20 mg once daily, increased as necessary after 3 weeks to a maximum of 80 mg daily, usual maintenance dose range, 20–60 mg once daily.

» Elderly: Initially 20 mg once daily, increased as necessary after 3 weeks to a maximum of 60 mg daily, maintenance dose range, 20–40 mg once daily.

Paediatric

Major Depression, Oral:

Child 8–12 years: 10 mg once daily increased after 1–2 weeks if necessary to a maximum of 20 mg once daily.

Contraindications: Use of MAOIs such as phenelzine within 14 days of starting fluoxetine (potentially fatal

reactions may occur), do not use MAOIs for at least 5 weeks after fluoxetine has been discontinued.

manic phase.

Precautions: epilepsy, cardiac disease, bleeding disorders, diabetes mellitus, susceptibility to closed-angle glaucoma, history of mania (discontinue if patient entering manic phase), concurrent electroconvulsive therapy (prolonged seizures reported), hepatic impairment, avoid abrupt withdrawal (see below), pregnancy and breastfeeding, increased risk of suicidal thinking and behaviour in children and adolescents, risk should be considered when prescribing, may cause decreased growth possibly by suppression of growth hormone secretion.

Skilled tasks: Warn patient or Caregiver about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery.

Withdrawal: Dizziness, nausea, anxiety, headaches, paraesthesia, sleep disturbances, fatigue, agitation, tremor and sweating may occur if withdrawn abruptly.

Hepatic impairment: Reduce dose or administer on alternate days. Avoid in severe impairment.

Renal impairment: Dose reduction not necessary.

Pregnancy: Foetal risk cannot be ruled out.

Breastfeeding: Present in milk, use only if potential benefit outweighs risk.

Adverse effects: Nausea, agitation, insomnia, drowsiness, tremor, dry mouth, diarrhoea, dizziness, headache, sweating, weakness, anxiety, weight gain or loss, sexual dysfunction, rhinitis, myalgia, rash, chills, euphoria, yawning.

extrapyramidal reactions (including tardive dyskinesia and dystonia), sedation, confusion, palpitations, tachycardia, hypotension, hyponatraemia (as part of SIADH), abnormal platelet aggregation/haemorrhagic complications (e.g., bruising, epistaxis, GI and vaginal bleeding), alopecia, changes in blood sugar, serotonin syndrome.

elevated liver enzymes, hepatitis, hepatic failure, galactorrhoea, blood dyscrasias, seizures, akathisia, paraesthesia, taste disturbance, toxic epidermal necrolysis and neuroleptic malignant syndrome.

Interaction with other medicines (*indicates serious):

* Acetylsalicylic acid: increased risk of bleeding.

* Artemether + lumefantrine: avoid concomitant use.

* Carbamazepine: plasma concentration of carbamazepine increased.

* Erythromycin: increased risk of cardiotoxicity.

Ethanol: possible increased sedation.

* Haloperidol: plasma concentration of haloperidol increased.

*ibuprofen: increased risk of bleeding.

* Lithium: increased risk of CNS effects (lithium toxicity reported).

* MAOIs: the cumulative effects on serotonin metabolism can cause serotonin toxicity, combination contraindicated. Fatal reactions have occurred.

* Metoclopramide: increased risk of extrapyramidal adverse effects and neuroleptic malignant syndrome.

Phenobarbital: antagonism of anticonvulsive effect (convulsive threshold lowered).

* Phenytoin: plasma concentration of phenytoin increased.

* Phenelzine: concurrent use contraindicated, potentially fatal interaction.

Ritonavir: plasma concentration of fluoxetine possibly increased.

* Tranylcypromine: concurrent use contraindicated, potentially fatal interaction.

* Warfarin: anticoagulant effect possibly enhanced.

Notes:

- Consider the long duration of action of fluoxetine when adjusting dosage.
- Warning: Clinical worsening of depression or suicidal ideation may occur.
- WHO age restriction: > 8 years.
- Family members and caregivers of children or adolescents prescribed fluoxetine for depression should be warned to observe for signs of clinical worsening of depression and suicidality, particularly in the first few months of therapy.

Mirtazapine

ATC code: N06AX11

Tablet, 15 mg, LOU 5

Indications and dose

Adult

Management of depression complicated by anxiety or trouble sleeping, oral: 15 mg once a day (every bedtime), may increase no more frequently than every 1 to 2 weeks, not to exceed 45 mg daily.

Paediatric: Not indicated for use in children.

Contraindication: Hypersensitivity**,** within 14 days of administration of MAOIs (serotonin syndrome), Patients receiving linezolid or methylene blue IV

Precautions: Cardiac disorders, diabetes mellitus, elderly, history of bipolar depression, history of seizures, history of urinary retention, hypotension, psychoses (may aggravate psychotic symptoms), susceptibility to angle- closure glaucoma.

Hepatic impairment: Dose adjustment not necessary. Use with caution in severe impairment.

Renal impairment: eGFR <30 mL/min/1.73 m2: Initial: 7.5 to 15 mg once daily, titrate slowly with close monitoring for adverse effects

Pregnancy: Use with caution. Monitor neonate for withdrawal effect.

Breastfeeding: Present in milk, use only if potential benefit outweighs risk.

Adverse effects: Common: Somnolence, Weight gain, Xerostomia, Increased appetite, Constipation, Asthenia, Weakness, Weight gain, Dizziness, Serum TGs

increased, Dream disorder, Disturbance in thinking, ALT increased, Peripheral edema, Myalgia, Confusion, Urinary frequency, Tremor, Back pain, Dyspnea, Hallucinations, mania, movement disorders, oral disorders, syncope

Interaction with other medicines (*indicates serious):

itraconazole, ketoconazole, voriconazole, Apalutamide, Cobicistat, Enzalutamide, HIV-protease inhibitors, Macrolides (clarithromycin), Mitotane, Rifampicin,*bromperidol, *thalidomide, *selegiline, warfarin

Notes:

- When discontinuing antidepressant treatment that has lasted for >3 weeks, gradually taper the dose (e.g., over 2 to 4 weeks) to minimize withdrawal symptoms and detect reemerging symptoms
- Has a lower incidence of sexual dysfunction than SSRIs

Venlafaxine

ATC code: N06AX16

Tablets, 37.5 mg, 75mg, LOU 4

Indications and dose

Adult

Treatment of major depressive episodes and for the prevention of recurrence of major depressive episodes, oral: Initially 75 mg daily in 2 divided doses, then increased if necessary up to 375 mg daily, dose to be increased, if necessary, at intervals of at least 2 weeks, faster dose titration may be necessary in some patients; maximum 375 mg per day

Paediatric: Not recommended for use in children and adolescents.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia. Venlafaxine must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Venlafaxine must be discontinued for at least 7 days before starting treatment with an irreversible MAOI. Contraindicated in uncontrolled hypertension.

Precautions: Conditions associated with high risk of cardiac arrhythmia, diabetes, heart disease (monitor blood pressure), history of bleeding disorders, history of epilepsy, history or family history of mania and susceptibility to angle-closure glaucoma

Hepatic impairment: Manufacturer advises caution (inter-individual variability in clearance; limited information available in severe impairment). Consider dose reduction of 50% in mild to moderate impairment and of more than 50% in severe impairment.

Renal impairment: Use with caution (inter-individual variability in clearance). Use half normal dose if eGFR less than 30 mL/minute/1.73 m2

Pregnancy: Avoid unless potential benefit outweighs risk—toxicity in animal studies. Risk of withdrawal effects in neonate.

Breastfeeding: Present in milk - avoid.

Adverse effects: Common or very common: Anxiety, decreased appetite, arrhythmias, asthenia, chills, confusion, constipation, depersonalization, diarrhea, dizziness, dry mouth, dyspnea, headache, hot flush, hypertension, menstrual cycle irregularities, movement disorders, muscle tone increased, mydriasis, nausea, palpitations, paraesthesia, sedation, sexual dysfunction, skin reactions, sleep disorders, sweat changes, taste altered, tinnitus, tremor, urinary disorders, vision disorders, vomiting, weight changes, yawning. Uncommon: Alopecia, angioedema, apathy, abnormal behavior, derealisation, hallucination, hypotension, mood altered, photosensitivity reaction, syncope. Rare or very rare: Agranulocytosis, angle closure glaucoma, bone marrow disorders, delirium, hepatitis, hyponatraemia, neuroleptic malignant syndrome, neutropenia, pancreatitis, interval prolongation, respiratory disorders, rhabdomyolysis, seizure, serotonin syndrome, severe cutaneous adverse reactions (SCARs), SIADH, thrombocytopenia. Frequency not known: Suicidal behaviors, vertigo, withdrawal syndrome.

Interactions with other medicines: MAOIs, ethanol, medicines that prolong the QT interval, ketoconazole (CYP3A4 inhibitor) and other medicines metabolized by Cytochrome P450 Isoenzymes, Lithium, diazepam, imipramine, haloperidol, risperidone, metoprolol, indinavir, oral contraceptives.

Notes: Venlafaxine is associated with a higher risk of withdrawal effects compared with other antidepressants.

25.2.2.Medicines Used In Bipolar Disorders

Carbamazepine

ATC code: N03AF01

Tablet (cross-scored), 200 mg, LOU 2

Tablet (controlled release), 200mg, LOU 4

Indications and dose

Adult

Prophylaxis of bipolar disorder, oral: Initially 400 mg daily in divided doses increased until symptoms are controlled up to a maximum of 1.6 g daily, usual maintenance dose range, 400–600 mg daily.

Paediatric: Used for other indications

Contraindications: Atrioventricular conduction abnormalities, history of bone marrow depression, porphyria.

Precautions: Hepatic impairment, renal impairment, cardiac disease, skin reactions. history of blood disorders (monitor blood counts before and during treatment), glaucoma, pregnancy (risk of neural tube defects and neonatal bleeding,), breastfeeding, avoid sudden withdrawal, Blood, hepatic or skin disorders. Patients or their Caregivers should be told how to recognize signs of blood, liver, or skin disorders,

and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Leukopenia which is severe, progressive and associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative).

Skilled tasks: May impair ability to perform skilled tasks, for example operating machinery or driving. Adverse effects), history of blood disorders (monitor blood counts before and during treatment), glaucoma, avoid sudden withdrawal.

Hepatic impairment: Metabolism impaired in advanced liver disease.

Renal impairment: Use with caution.

Severe impairment: administer 75% of dose and monitor serum levels.

Pregnancy: Not recommended in pregnancy

Breastfeeding: Amount in breast milk might be too small to be harmful. Monitor infant for adverse effects.

Adverse effects: Common: Drowsiness, ataxia, dizziness, blurred vision, diplopia, headache (all dose related), rash, dry mouth, abdominal pain, nausea, vomiting, anorexia, diarrhoea, constipation, asymptomatic hyponatraemia, leukopenia, thrombocytopenia, increased liver enzymes (usually not clinically significant).

Rare: Severe skin reactions (see below), SLE, agranulocytosis, aplastic anaemia, cholestatic jaundice, multi-organ hypersensitivity syndrome (including fever, lymphadenopathy, haematological abnormalities, hepatitis), psychosis, arrhythmia, orofacial dyskinesia, hepatitis, gynaecomastia, galactorrhoea, aggression, jaundice, osteomalacia, confusion, arthralgia.

Severe skin reactions Include exfoliative dermatitis, SJS and toxic epidermal necrolysis, may also occur as part of multi-organ hypersensitivity syndrome.

Serious reactions mostly occur within the first few months of treatment and are more common in those with the HLA-B*1502 allele, which occurs predominantly in people of Han Chinese or Thai ancestry.

Interaction with other medicines (*indicates serious):

* Amitriptyline: antagonism of anticonvulsant effect (seizure threshold lowered), accelerated metabolism of amitriptyline (reduced plasma concentration, reduced antidepressant effect).

Chloroquine: possibly increased risk of seizures.

* Chlorpromazine: antagonism of anticonvulsant effect (seizure threshold lowered).

Ciclosporin: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).

* Dexamethasone: accelerated metabolism of dexamethasone (reduced effect).

Doxycycline: accelerated metabolism of doxycycline (reduced effect).

* Erythromycin: increased plasma carbamazepine concentration.

Ethosuximide: may be enhanced toxicity without corresponding increase in anticonvulsant effect, plasma concentration of ethosuximide possibly reduced.

Fluoxetine: plasma concentration of carbamazepine increased.

Furosemide: increased risk of hyponatraemia.

* Haloperidol: antagonism of anticonvulsant effect (seizure threshold lowered), metabolism of

haloperidol accelerated (reduced plasma concentration).

Hydrochlorothiazide: increased risk of hyponatraemia.

* Hydrocortisone: accelerated metabolism of hydrocortisone (reduced effect).

*isoniazid: increased plasma carbamazepine concentration (also isoniazid hepatotoxicity possibly increased).

Levothyroxine: accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism).

* Lopinavir: possibly reduced plasma lopinavir concentration.

Mebendazole: reduced plasma mebendazole concentration (possibly increase mebendazole dose

for tissue infection).

Mefloquine: antagonism of anticonvulsant effect.

Miconazole: plasma concentration of carbamazepine possibly increased.

Phenobarbital: may be enhanced toxicity without corresponding increase in anticonvulsant effect, reduced plasma concentration of carbamazepine. Incidence of serious adverse effects such as Stevens- Johnson syndrome may increase when used in combination.

* Phenytoin: may be enhanced toxicity without corresponding increase in anticonvulsant effect, plasma concentration of phenytoin often lowered but may be raised, plasma concentration of carbamazepine often lowered. Incidence of serious adverse effects such as SJS may increase when used in combination.

Praziquantel: plasma praziquantel concentration reduced.

* Prednisolone: accelerated metabolism of prednisolone (reduced effect).

* Ritonavir: plasma concentration possibly increased by ritonavir.

Saquinavir: possibly reduced plasma saquinavir concentration. Spironolactone: increased risk of hyponatraemia.

Valproic acid: may be enhanced toxicity without corresponding increase in anticonvulsant effect, reduced plasma concentration of valproic acid, plasma concentration of active metabolite of carbamazepine increased.

Vecuronium: antagonism of muscle relaxant effect (recovery from neuromuscular blockade accelerated).

* Warfarin: accelerated metabolism of warfarin (reduced anticoagulant effect).

Notes:

» Therapeutic drug monitoring is available for carbamazepine but routine monitoring is not required for the majority of patients.

- Plasma concentration for optimum response 4–12 mg/L (17–50 micromol/L).
- monitor patients for changes in behaviour that could indicate the emergence, or worsening, of suicidal thoughts or behaviour or depression.
- Rare but potentially fatal blood cell abnormalities (aplastic anaemia and agranulocytosis) have been reported in association with carbamazepine treatment. These mostly occur in the first 3–4 months of treatment.
- SJS and toxic epidermal necrolysis may occur.
- Patients and/or caregivers should be told how to recognize possible blood disorders and severe skin conditions, and to seek medical attention should they occur.

Divalproex Sodium

ATC code: N03AG01

Tablet, 500 mg, 750 mg, LOU 4

Indications and dose

Adult

Treatment of manic episodes associated with bipolar disorder, Prevention of recurrence of bipolar disorder, oral: start with 200 mg 2 times daily. Increase if necessary until the optimal dose for the individual patient is reached, usually around 500 mg 2 times daily (max. 1000 mg 2 times daily).

Paediatric: Used for other indications.

Contraindication: Hypersensitivity, Liver disease, significant hepatic impairment, Urea cycle disorders, Mitochondrial disorders caused by mutations in mitochondrial DNA polymerase-gamma (e.g., Alpers-Huttenlocher Syndrome) and children <2 years of age who are suspected of having a POLG-related disorder

Migraine headache prevention in women who are pregnant or plan to become pregnant

Precautions: Beers criteria, avoid use in patients with history of falls or fractures

Concomitant use in carbapenem antibiotics,

Abrupt discontinuation in epileptic patients may precipitate life threatening status epilepticus

Hepatic impairment: Not indicated for use in mild to moderate impairment. Contraindicated in severe impairment.

Renal impairment: Use with caution in CrCl<10 mL/min

Pregnancy: Contraindicated in pregnancy.

Breastfeeding: Monitor infant for adverse effects.

Adverse effects: Nausea, Headache, Asthenia, Vomiting, Somnolence, Tremor, Dizziness, Abdominal pain, Diplopia, Diarrhea, Anorexia, Amblyopia/ blurred vision, Flu syndrome, Infection, Dyspepsia, Ataxia, Nystagmus, Fever, Emotional lability, Thinking abnormal, Alopecia, Weight loss, Constipation, Amnesia, Bronchitis, Rhinitis

Interaction with other medicines (*indicates serious):

Doripenem, Lamotrigine, Meropenem, Olanzapine, *bromperidol, *azelastine, bupivacaine, buprenorphine, carbamazepine, carbapenems, methotrexate, *thalidomide.

Lamotrigine

ATC code: N03AX09

Tablet (chewable/dispersible), 25 mg, LOU 5

Tablet, 25 mg, 100 mg, LOU 5

Indications and dose

Adult

Monotherapy or adjunctive therapy of bipolar disorder (without enzyme inducing drugs) without valproate, oral: Initially 25 mg once daily for 14 days, then 50 mg daily in 1–2 divided doses for further 14 days, then 100 mg daily in 1–2 divided doses for further 7 days; maintenance 200 mg daily in 1–2 divided doses, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimens — consult product literature, dose titration should be repeated if restarting after interval of more than 5 days; maximum 400 mg per day

Adjunctive therapy of bipolar disorder with valproate, oral: Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then 50 mg daily in 1–2 divided doses for further 7 days; maintenance 100 mg daily in 1–2 divided doses, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimens— consult product literature, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day

Adjunctive therapy of bipolar disorder (with enzyme inducing drugs) without valproate, oral: Initially 50 mg once daily for 14 days, then 50 mg twice daily for further 14 days, then increased to 100 mg twice daily for further 7 days, then increased to 150 mg twice daily for further 7 days; maintenance 200 mg twice daily, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimens—consult product literature, dose titration should be repeated if restarting after interval of more than 5 days

Paediatric

Not recommended – not licensed

For contraindications, precautions, hepatic and renal impairment, pregnancy and breastfeeding, adverse effects, interactions, and notes: *See Lamotrigine monograph in section 6. Anticonvulsants/Antiepileptics*

Lithium Carbonate

ATC code: N05AN01

Tablet (scored), 400 mg, LOU 6

Tablet (m/r), 400 mg, LOU 6

Indications and dose:

Adult

Treatment of mania (general guidelines only, see also

notes), oral: 0.6–1.8 g daily

Prophylaxis of mania, bipolar disorder and recurrent depression (general guidelines only, see also note below), oral: 0.6–1.2 g daily.

» Elderly: *Treatment of mania, Prophylaxis of mania, bipolar disorder and recurrent depression (general guidelines only, see also notes), oral*: 300–900 mg daily for treatment and prophylaxis

Paediatric

Treatment of bipolar disorder, Oral: (Immediate release formulation)

Children ≥7 years and Adolescents:

Patient weight <30 kg: Initial: 300 mg twice daily, increase dose at weekly intervals in 300 mg/day increments as tolerated to clinical response and goals based on type of therapy (acute or maintenance).

Acute therapy: Titrate dose to 600 to 1,500 mg/day in divided doses and target serum lithium concentration of 0.8 to 1.2 mEq/L,

Maintenance therapy: Titrate dose to 600 to 1,200 mg/day in divided doses and target serum trough concentration of 0.8 to 1 mEq/L as tolerated.

Patient weight ≥30 kg: Initial: 300 mg 3 times daily, increase dose in 300 mg/day increments every 3 days as tolerated to clinical response and goals based on type of therapy (acute or maintenance).

Acute therapy: Titrate dose to 600 mg twice or 3 times daily and target serum lithium concentration of 0.8 to 1.2 mEq/L,

Maintenance therapy: Titrate dose to 300 to 600 mg twice or 3 times daily and target serum trough concentration of 0.8 to 1 mEq/L as tolerated,

Contraindications: renal impairment, cardiac insufficiency, conditions with sodium imbalance such as Addison disease.

Precautions: measure serum lithium concentration about 4 days after starting treatment, then weekly until stabilized, and then at least once every

3 months, monitor renal function and thyroid function every 6–12 months on stabilized regimens (risk of hypothyroidism, see also note on Patient advice below), maintain adequate fluid and sodium intake, reduce dose or discontinue in diarrhoea, vomiting, and intercurrent infection (especially if associated with profuse sweating), psoriasis (risk of exacerbation), pregnancy and breastfeeding, the elderly (reduce dose), diuretic treatment, myasthenia gravis, surgery, avoid abrupt withdrawal

Hepatic impairment: Dose adjustment not necessary

Renal impairment: CrCl 30 to 89 mL/min: Initiate therapy with low dose, titrate slowly with frequent monitoring, CrCl < 30 mL/min: Avoid use.

Pregnancy: Avoid use in first trimester. suspend 24 to 48 hours prior to delivery or at the onset of labor when delivery is spontaneous, then restart when the patient is medically stable after delivery.

Breastfeeding: Avoid breastfeeding.

Adverse effects: GI disturbances, fine tremor, renal impairment (particularly impaired urinary concentration and polyuria), polydipsia, leukocytosis, weight gain and oedema (may respond to dose reduction), hyperparathyroidism and hypercalcaemia reported, signs of intoxication include blurred vision, muscle weakness, increasing GI disturbances (anorexia, vomiting, diarrhoea), increased CNS disturbances (mild drowsiness and sluggishness, increasing to giddiness with ataxia, coarse tremor, lack of co-ordination, and dysarthria) and require withdrawal of treatment, goitre, raised antidiuretic hormone concentration, hypothyroidism, hypokalaemia, ECG changes, and kidney changes also reported, with severe overdosage (serum concentrations above 2 mmol/L), hyperreflexia and hyperextension of the limbs, convulsions, toxic psychoses, syncope, renal failure, circulatory failure, coma, and occasionally death.

Interaction with other medicines (*indicates serious):

* Acetazolamide, Excretion of lithium increased

Alcuronium, Enhanced muscle relaxant effect

Amiloride, Reduced lithium excretion (increased plasma lithium concentration and risk of toxicity)

Amitriptyline, Risk of toxicity

Carbamazepine, Neurotoxicity may occur without increased plasma lithium

concentration

Chlorpromazine, Increased risk of extrapyramidal effects and possibility of

neurotoxicity

Clomipramine, Risk of toxicity

* Enalapril, Enalapril reduces excretion of lithium (increased plasma lithium concentration)

* Fluoxetine, Increased risk of CNS effects (lithium toxicity reported)

Fluphenazine, Increased risk of extrapyramidal effects and possibility of neurotoxicity

* Furosemide, Reduced lithium excretion (increased plasma lithium

concentration and risk of toxicity), furosemide safer than hydrochlorothiazide

Haloperidol, Increased risk of extrapyramidal effects and possibility of neurotoxicity

* Hydrochlorothiazide, Reduced lithium excretion (increased plasma lithium

concentration and risk of toxicity), furosemide safer than hydrochlorothiazide

*ibuprofen, Reduced excretion of lithium (increased risk of toxicity)

* Methyldopa, Neurotoxicity may occur without increased plasma lithium concentration

Metronidazole, Increased lithium toxicity reported

Neostigmine, Antagonism of effect of neostigmine

Phenytoin, Neurotoxicity may occur without increased plasma lithium

concentration

Pyridostigmine, Antagonism of effect of pyridostigmine

Sodium hydrogen

Carbonate, Increased excretion of lithium (reduced plasma lithium concentration)

* Spironolactone, Reduced lithium excretion (increased plasma lithium concentration and risk of toxicity)

Suxamethonium, Enhanced muscle relaxant effect

Vecuronium, Enhanced muscle relaxant effect

Verapamil, Neurotoxicity may occur without increased plasma lithium Concentration

Notes:

- Different preparations vary widely in bioavailability, a change in the preparation used requires the same precautions as initiation of treatment.
- Dosage should be adjusted to achieve a serum lithium concentration of 0.4–1 mmol/L (aim for the lower end of the range for maintenance therapy and in the elderly) based on samples taken 12 hours after a dose, serum concentrations should be measured 4–7 days after starting treatment, then every week until dosage has remained unchanged for 4 weeks, and then every 3 months.
- Dosage regimens: For dose information for a specific preparation, consult manufacturer's literature.
- Patient advice: Patients should maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake. Patients should be advised to seek medical attention if symptoms of hypothyroidism (for example, feeling cold, lethargy) develop (women are at greater risk).

Quetiapine

(See above) Section 25.1

25.3. Medicines For Anxiety Disorders

Alprazolam

ATC code: N05BA12

Tablet, 0.25mg, 0.5mg, LOU 3

Indications and dose

Adult

Short-term symptomatic treatment of anxiety (only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress), oral: 250–500 micrograms three times a day, increased if necessary up to 3 mg daily, for a maximum of 2-4 weeks. For debilitated patients, use elderly dose.

Elderly: 250 micrograms 2–3 times a day, increased if necessary up to 3 mg daily for a maximum of 2-4 weeks.

Paediatric

The safety and efficacy of alprazolam in children and adolescents below the age of 18 years have not been established. No data are available.

Contraindications: Respiratory depression, sleep apnoea syndrome and severe hepatic insufficiency. Hypersensitivity to benzodiazepines, alprazolam, or to any of the excipients. Myasthenia gravis

Precautions: Muscle weakness, organic brain changes

Hepatic impairment: In advanced hepatic impairment decrease initial dose to 0.25 mg every 8-12 hours.

Renal impairment: Use with caution. No sufficient data

Pregnancy: Avoid in pregnancy.

Breastfeeding: Benzodiazepines are present in milk, and should be avoided, if possible, during breast-feeding.

Adverse effects: Common or very common: Decreased appetite, impaired concentration, constipation, dermatitis, dry mouth, memory loss, movement disorders, sexual dysfunction, weight changes. Uncommon: Irregular menstruation, urinary incontinence. Frequency not known: Angioedema, autonomic dysfunction, gastrointestinal disorder, hepatic disorders, hyperprolactinaemia, peripheral oedema, photosensitivity reaction, psychosis, suicide, abnormal thinking.

Interactions with other medicines: Opioids: The concomitant use with opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. Concomitant intake with alcohol is not recommended.

CYP3A Inhibitors: Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) may increase the concentration of alprazolam and enhance its activity. The co-administration of alprazolam with ketoconazole, itraconazole, or other azole-type antifungals is not recommended. Caution is recommended when alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin, clarithromycin and troleandomycin.

CYP3A4 Inducers: Since alprazolam is metabolized by CYP3A4, inducers of this enzyme may enhance the metabolism of alprazolam. Interactions involving HIV protease inhibitors (e.g., ritonavir) and alprazolam are complex and time dependent.

Digoxin: Increased digoxin concentrations have been reported when alprazolam was given, especially in elderly (>65 years of age). Patients who receive alprazolam and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

Bromazepam

ATC code: N05BA08

Tablet (scored), 3 mg, LOU 4

Indications and dose

Adult

Anxiety with agitation for short-term or immediate symptom relief until concurrent therapy is effective (Note: Use is restricted), oral: Initial: 6 to 18 mg/day in equally divided doses. Initial course of treatment should not last longer than 1 week without reassessment of the need for a limited extension.

Paediatric: Not indicated for use in children

Contraindication: Elderly, history of alcohol or other substance abuse, pregnancy, children

Precautions: Patients with impaired liver or kidney function, muscle weakness, debilitated patients, respiratory disease, marked personality disorder, breastfeeding, avoid prolonged use and abrupt withdrawal, porphyria.

Hepatic impairment: contraindicated in severe impairment.

Renal impairment: Dose adjustment not necessary.

Pregnancy: Foetal risk cannot be ruled out.

Breastfeeding: Not recommended while breastfeeding.

Adverse effects:

Nausea, vomiting, diarrhea, constipation, headache, dizziness, mood changes, muscle weakness, hypersensitivity (over- responsiveness) to sensory stimuli (light, sound and pressure), confusion, insomnia, hallucinations, emotional problems, memory impairment, seizures, allergy

Interaction with other medicines (*indicates serious):

antipsychotic, *opioid analgesics, anticonvulsants, antihistamines, olanzapine, *azelastine,

Notes:

- drowsiness may affect performance of skilled tasks (e.g., driving), effects of alcohol enhanced.
- In patients receiving extended- or higher-dose benzodiazepine therapy, unless safety concerns require a more rapid withdrawal, gradually withdraw to detect reemerging symptoms and minimize rebound and withdrawal symptoms. Taper total daily dose by 10% to 50% every 1 to 2 weeks based on response and tolerability

Escitalopram

(*See above*) Section 25.2.1

Mirtazapine

(*See above*) Section 25.2.1

Paroxetine

ATC code: N06AB05

Tablet 20mg, LOU 4

Indications and dose

Adult

Treatment of major depression, social anxiety disorder, post-traumatic stress disorder and generalised anxiety disorder, oral: 20 mg daily, dose to be taken in the morning, no evidence of greater efficacy at higher doses; maximum 50 mg per day.

Elderly: 20 mg daily, dose to be taken in the morning, no evidence of greater efficacy at higher doses; maximum 40 mg per day.

Obsessive-compulsive disorder, oral: Initially 20 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually, increased to 40 mg daily, no evidence of greater efficacy at higher doses; maximum 60 mg per day.

Elderly: Initially 20 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually; maximum 40 mg per day.

Panic disorder, oral: Initially 10 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually, increased to 40 mg daily, no evidence of greater efficacy at higher doses; maximum 60 mg per day.

Elderly: Initially 10 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually; maximum 40 mg per day.

Paediatric: Paroxetine should not be used in the treatment of children and adolescents under the age of 18 years.

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Contraindicated in combination with monoamine oxidase inhibitors (MAOIs). Paroxetine should not be used in combination with thioridazine, because, as with other medicinal products, which inhibit the hepatic enzyme CYP450 and CYP2D6, paroxetine can elevate plasma levels of thioridazine. Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death. Paroxetine should not be used in combination with pimozide.

Precautions: Achlorhydria or high gastric pH causes reduced absorption of the oral suspension.

Hepatic impairment: Manufacturer advises dose adjustments to the lower end of the range.

Renal impairment: Use with caution if creatinine clearance less than 30 mL/minute.

Pregnancy: Increased risk of congenital malformations, especially if used in the first trimester.

Breastfeeding: Present in milk but amount too small to be harmful.

Adverse effects: Common or very common: Blurred vision. Uncommon: Impaired diabetic control. Rare or very rare: Acute glaucoma, hepatic disorders, peripheral oedema

Interactions with other medicines: May interact with serotonergic medicinal products, pimozide, drug metabolising enzymes, neuromuscular blockers, fosamprenavir/ritonavir, procyclidine, CYP2D6 inhibitory potency of paroxetine, anticonvulsants, alcohol, oral anticoagulants, pravastatin, NSAIDs and acetylsalicylic acid, and other antiplatelet agents.

Propranolol

ATC code: C07AA05

Tablet, 40 mg (as HCl), LOU 3

Indications and dose

Adult

Anxiety with symptoms such as palpitation, sweating and tremor, oral: 40 mg once daily, then increased if necessary to 40 mg 3 times a day.

Paediatric: Not licensed for use in children for this indication

Contraindications: Asthma, history of bronchospasm, uncontrolled heart failure, marked bradycardia, hypotension, sick sinus syndrome, second or third-degree atrioventricular block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease, phaeochromocytoma.

Precautions: Avoid abrupt withdrawal, first-degree atrioventricular block, portal hypertension, diabetes mellitus, history of obstructive airways disease, renal impairment, liver disease, myasthenia gravis, history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline)).

Renal impairment: Severe: start with small dose, higher plasma concentrations after oral administration, may reduce renal blood flow and adversely affect renal function.

Hepatic impairment: Reduce oral dose.

Adverse effects: Nausea, diarrhoea, fatigue, insomnia, nightmares, dyspnoea, bronchospasm, peripheral vasoconstriction, exacerbation of Raynaud syndrome, bradycardia, heart failure, hypotension, conduction disorders. Rash, exacerbation of psoriasis, muscle cramp, dry eyes. Hypersensitivity reaction, thrombocytopenic purpura, liver function abnormality, alopecia, cardiac arrest.

Interactions with other medicines (*indicates serious): *Bupivacaine, *chlorpromazine, oral contraceptives, dexamethasone, diazepam, digoxin, enalapril, *epinephrine, furosemide, halothane, hydrochlorothiazide, hydrocortisone, ibuprofen, insulins, ketamine, *lidocaine, mefloquine, neostigmine, *nifedipine, nitrous oxide, prednisolone, *procainamide, pyridostigmine, *quinidine, rifampicin, sodium nitroprusside, spironolactone, suxamethonium, thiopental, vecuronium, *verapamil.

Notes: Advise patient or caregiver not to discontinue abruptly. Given with food.

25.4. Medicines Used In Obsessive-Compulsive Disorders

Clomipramine

ATC code: N06AA04

Capsule, 25 mg (HCl), LOU 4

Indications and dose

Adult

Phobic and obsessional states, oral: Initially 25 mg daily, usually at bedtime (10 mg daily in the elderly) increased over 2 weeks to 100–150 mg daily.

Paediatric

Obsessive-compulsive disorder, treatment, oral:

Children ≥10 years and Adolescents: Initially 25 mg daily, gradually increase as tolerated over the first 2 weeks to 3 mg/kg/day or 100 mg daily (whichever is less) in divided doses (may be divided with meals)

Maintenance: May further increase over next several weeks up to maximum daily dose: 3 mg/kg/**day** or 200 mg/**day** (whichever is less), after titration, may give as a single once daily dose at bedtime

Contraindications: recent MI, arrhythmias (especially heart block), manic phase in bipolar disorders, severe liver disease, children below 10years, porphyria.

Precautions: cardiac disease (see also Contraindications above), history of epilepsy, pregnancy and breastfeeding, the elderly, hepatic impairment, thyroid disease, phaeochromocytoma, history of mania, and psychoses (may aggravate psychotic symptoms), angle-closure glaucoma, history of urinary retention, concurrent electroconvulsive therapy, avoid abrupt withdrawal, anaesthesia (increased risk of arrhythmias and hypotension),

Skilled tasks: May impair ability to perform skilled tasks, for example operating machinery or driving.

Hepatic impairment: Use with caution in hepatic impairment

Renal Impairment: Use with caution in significant renal impairment.

Pregnancy: Neonatal withdrawal symptoms reported if used during third trimester

Breastfeeding: The amount secreted into breast milk is too small to be harmful.

Adverse effects: sedation, dry mouth, blurred vision (disturbance of accommodation, increased intraocular pressure), constipation, nausea, difficulty in micturition, cardiovascular adverse effects particularly with high dosage including ECG changes, arrhythmias, postural hypotension, tachycardia, and syncope, sweating, tremor, rash, hypersensitivity reactions (urticaria including photosensitivity), behavioural disturbances, hypomania or mania, confusion or delirium (particularly in the elderly), headache, interference with sexual function, blood sugar changes, increased appetite and weight gain (occasional weight loss), endocrine adverse effects such as testicular enlargement, gynaecomastia, and galactorrhoea, convulsions, movement disorders and dyskinesias, dysarthria, paraesthesia, taste disturbances, tinnitus, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (may be due to SIADH), abnormal liver function test, diarrhoea, hair loss reported.

Interaction with other medicines:

See amitriptyline 25.2.1.1 above

25.5. Medicines For Disorders Due to Psychoactive Substance Abuse

These products are to be used under close supervision within substance dependency treatment programmes

Acamprosate Calcium

ATC code: N07BB03

Tablet, 333mg, LOU 6

Indications and dose

Adult

Maintenance of abstinence in alcohol-dependent patients, oral:

Adult 18–65 years (body weight <60 kg): 666 mg once daily at breakfast and 333 mg twice daily at midday and at night

Adult 18–65 years (body weight ≥60 kg): 666 mg three times a day

Elderly >65years: Not recommended.

Paediatric:

Acamprosate should not be administered to children and adolescents.

Contraindications: Hypersensitivity to the active substance or to any of the excipients, breast-feeding women, and patients with renal impairment (serum creatinine >120 micromol/l)

Precautions: Continued alcohol abuse (risk of treatment failure)

Hepatic impairment: Manufacturer advises caution in severe hepatic failure. No information available.

Renal impairment: Avoid in renal impairment if serum-creatinine greater than 120 micromol/L.

Pregnancy: Manufacturer advises avoid unless potential benefit outweighs risk.

Breastfeeding: Avoid. No adequate data

Adverse effects: Abdominal pain, diarrhoea, flatulence, nausea, sexual dysfunction, skin reactions, vomiting.

Interactions with other medicines (*indicates serious): Limited data available.

Vitamins B and C

ATC code: A11EB

Injection (IV), 10 mL (2 × 5 mL amps), Contains ascorbic acid 500 mg, nicotinamide 160 mg, pyridoxine HCl 50 mg, riboflavin (as phosphate sodium) 4 mg and thiamine HCl 250 micrograms across the two 5-mL amps, LOU 4

Indications and dose

Adult

Rapid therapy of severe depletion/malabsorption of water-soluble vitamins B and C, especially in alcoholism, where a severe depletion of thiamine can lead to Wernicke's encephalopathy, IV:

2 to 3 pairs of 5 mL ampoules* (1 pair = amp 1 + amp 2) diluted with 50 mL to 100 mL infusion solution (physiological saline or glucose 5%) and administered over 30 minutes every 8 hours, or at the discretion of the physician.

10 mL solution from amp number 1	PLUS	10 mL solution from amp number 2
OR		
15 mL solution from amp number 1	PLUS	15 mL solution from amp number 2

Paediatric

Rapid therapy of severe depletion/malabsorption of water-soluble vitamins B and C, especially in alcoholism, where a severe depletion of thiamine can lead to Wernicke's encephalopathy, IV:

Child< 6 years: quarter of the adult dose

Child 6–10 years: third of the adult dose

Child 10–14 years: half to two thirds of the adult dose

14 years and over: as for the adult dose

Contraindication: Specific contraindications not determined

Precautions: Acidification of urine may occur and lead to precipitation of cysteine, urate, or oxalate stones. May cause acute and chronic oxalate nephropathy in long term administration of high doses.

Hepatic impairment: Dose adjustment not necessary

Renal impairment: Dose adjustment not necessary in mild to severe impairment. Use with caution in patients with renal impairment or patients prone to recurrent renal calculi, may have increased risk of developing acute or chronic oxalate nephropathy.

Pregnancy: Foetal risk cannot be ruled out

Breastfeeding: Infant risk cannot be ruled out

Adverse effects: Constipation, diarrhea, or upset stomach

Interaction with other medicines: antacids, bisphosphonates (for example, alendronate), levodopa, thyroid medications (for example, levothyroxine), antibiotics (for example, tetracyclines, quinolones such as ciprofloxacin).

Note:

» Confirm the route of administration in the manufacturer's literature before administration.

Buprenorphine

ATC code: N02AE01

Tablet (sublingual), 2 mg, 8 mg (as HCl), LOU 4

Indications and dose

Adult

RESTRICTED. For use in medically assisted therapy clinics for people who use drugs, sublingual: Induction (sublingual tablet), 8 mg on day 1, then 16 mg on day 2, continued over 3–4 days

Paediatric

Safety and efficacy in medically assisted therapy clinics for paediatrics not established

Contraindication: Hypersensitivity, Significant depression, Acute or severe bronchial asthma in an, unmonitored setting or in the absence of resuscitative equipment, Known or suspected GI obstruction, including paralytic ileus

Precautions: Impaired consciousness

Hepatic impairment: Use with caution. Avoid in severe impairment.

Renal impairment: Avoid use or reduce dose, opioid effects increased and prolonged, increased cerebral sensitivity.

Pregnancy: Foetal risk cannot be ruled out.

Breastfeeding: Present in low levels in breast milk. Monitoring Neonates should be monitored for drowsiness, adequate weight gain, and developmental milestones.

Adverse effects:

Headache, Withdrawal syndrome, Insomnia, Infection, Asthenia, Back pain, Nausea, Sweating, abdominal pain, Infection, Dizziness/vertigo, Hypoventilation,

constipation, hypotension

Interaction with other medicines (*indicates serious):

*Mesoridazine, Alprozalam, Aripiprazole, Azithromycin, Bedaquiline, Bromazepam, Carbazepine, Cetirizine, Chlorpromazine, Ciprofloxacin, Delamanid, Diazepam, Doxycycline, Ebastine, Efavirenz, Haloperidol, Halothane, Norfloxacin, Rifabutin, Rifampicin

Buprenorphine + Naloxone

ATC code: N07BC51

Tablets (sublingual), 2 mg + 500 micrograms (both as HCl), 8 mg + 2 mg (both as HCl), LOU 4

Indications and dose

Adult

Maintenance treatment of opioid dependence, sublingual:

A single daily dose adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone to a maximum of 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose.

Paediatric: Safety and efficacy in medically assisted therapy clinics for paediatrics not established

Contraindication: Hypersensitivity, Significant depression, Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, Known or suspected GI obstruction, including paralytic ileus

Hepatic impairment: Use with caution. Avoid in severe impairment.

Renal impairment: Avoid use or reduce dose, opioid effects increased and prolonged, increased cerebral sensitivity.

Use in pregnancy/breastfeeding: Limited data. Weigh benefits against possible risks.

Adverse effects: asthenia, chills, headache, infection, pain, constipation, insomnia, rhinitis, sweating nausea and vomiting

Interaction with other medicines:

Alcohol, non- benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids. Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir) Rifampin, carbamazepine, phenytoin

Notes:

» Buprenorphine and naloxone sublingual tablet should be used as part of a complete treatment plan that includes counseling and psychosocial support.

Bupropion

ATC code: N06AX12

Tablet, 150 mg, LOU 4

Indications and dose

Adult

Smoking cessation, oral: 150 mg daily for 3 days, THEN increase to 150 mg every 12 hours, should continue treatment for 7–12 weeks, if patient successfully quits after 7–12 weeks, consider ongoing maintenance therapy based on individual patient risk/benefit

Dosing considerations

» Begin therapy 1 week before target quit date (usually second week of treatment)

» May be used in combination with nicotine patch

Paediatric: Safety and efficacy not established

Contraindication:

Hypersensitivity to bupropion or other ingredients

History of anorexia/bulimia, patients undergoing abrupt discontinuation of ethanol or sedatives including anticonvulsants, barbiturates, or benzodiazepines

Co-administration of any other medications that contain bupropion, because seizures are dose dependent

Concurrent use with MAOIs

Precautions: elderly, predisposition to seizures (prescribe only if benefit clearly outweighs risk) including concomitant use of drugs that lower seizure threshold, alcohol abuse, history of head trauma, and diabetes, measure blood pressure before and during treatment.

Hepatic impairment: Use with caution. Avoid in severe cirrhosis

Renal impairment: Reduce dose to 150 mg daily.

Pregnancy: Foetal risk cannot be ruled out.

Breastfeeding: Infant risk cannot be ruled out.

Adverse effects: Headache, Dry mouth, Nausea, Weight loss, Insomnia, Agitation, Dizziness, Pharyngitis, Constipation, Infection, Abdominal pain, Anxiety, Diarrhea, Tinnitus, Tremor, Nervousness, Anorexia, Palpitation, Myalgia, Sweating, Rash, Sinusitis, Weight gain, Chest pain, Urinary frequency, Vaginal hemorrhage, Pruritus, Vomiting, Arthralgia, Flushing,

Migraine, Decreased memory, Irritability, Somnolence, Dysphagia, Arthritis, Paresthesia, Fever, Twitch

Interaction with other medicines: prochlorperazine, chlorpromazine, and other antipsychotic medications of the phenothiazine class. Additionally, persons who are withdrawing from benzodiazepines [for example, diazepam, alprazolam] are at increased risk for seizures. Carbamazepine, MAO inhibitors, warfarin

Methadone

ATC code: N07BC02

Concentrate for oral liquid: 5 mg/mL (as HCl), LOU 4

Indication and dose

Adult

Adjunct in treatment of opioid dependence, oral: initially 10–40 mg daily, increased by up to 10 mg daily (maximum weekly increase, 30 mg) until no signs of withdrawal or intoxication, usual maintenance dose in range, 60–120 mg daily,

Paediatric: Not recommended (see also under Precautions)

Contraindications: acute respiratory depression, acute alcoholism, risk of paralytic ileus, raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment).

Precautions: renal impairment, hepatic impairment, risk of toxicity in children and non-dependant adults or if tolerance incorrectly assessed in dependent adults, severe withdrawal symptoms on abrupt withdrawal, hypothyroidism, convulsive disorders, decreased respiratory reserve and acute asthma, hypotension, prostatic hypertrophy, pregnancy, breastfeeding, overdosage

Hepatic impairment: Consider dose reduction.

Renal impairment: Avoid use or reduce dose, opioid effects increased and prolonged and increased cerebral sensitivity occurs.

Pregnancy: Opioids may cause respiratory depression and psycho-physiologic effects in the neonate, newborns of mothers receiving opioids during pregnancy and/or labor should be monitored, Risk of neonatal opioid withdrawal syndrome.

Breastfeeding: Withdrawal symptoms in infant, breastfeeding is permissible during maintenance, but dose should be as low as possible and infant monitored to avoid sedation.

Adverse effects: nausea, vomiting, constipation, drowsiness, also dry mouth, anorexia, difficulty with micturition, spasm of urinary and biliary tract, bradycardia, tachycardia, palpitations, dysphoria, mood changes, decreased libido or potency, rash, urticaria, pruritus, sweating, headache, facial flushing, vertigo, postural hypotension, hypothermia, hallucinations, confusion, and miosis, respiratory depression, hypotension, and muscle rigidity (with larger doses).

Interaction with other medicines:

Abacavir, Plasma concentration of methadone possibly reduced

Alcohol, Enhanced hypotensive and sedative effects

Amitriptyline, Sedative effects possibly increased

Carbamazepine, Reduced plasma concentration of methadone

Chlorpromazine, Enhanced hypotensive and sedative effects

Clomipramine, Sedative effects possibly increased

Diazepam, Increased sedative effect

Efavirenz, Reduced plasma concentration of methadone

Fluphenazine, Enhanced hypotensive and sedative effects

Haloperidol, Enhanced hypotensive and sedative effects

Metoclopramide, Antagonism of effects of metoclopramide on GI activity

Nelfinavir, Reduced plasma concentration of methadone

Nevirapine, possibly reduced plasma concentration of methadone

Phenytoin, Accelerated metabolism of methadone (reduced effect and risk of withdrawal symptoms)

Rifampicin, Accelerated metabolism of methadone (reduced effect)

Ritonavir, Reduced plasma concentration of methadone

Zidovudine, possibly increased plasma concentration of zidovudine

Notes:

- The final strength of the methadone mixture to be dispensed to the patient should be specified on the prescription. Care is required in prescribing and dispensing the correct strength because any confusion could lead to an overdose, this preparation should be dispensed only after dilution as appropriate.
- Drug subject to international control under the Single Convention on Narcotic Drugs (1961).
- Methadone is a representative opioid agonist for use in opioid dependence. Bupremorphine can serve as an alternative.
- Incompatibility: Syrup preserved with hydroxybenzoate (parabens) esters may be incompatible with methadone HCl.

Naltrexone

ATC code: N07BB04

Tablet, 50 mg (as HCl), LOU 4

Injection (IM, suspension for extended release), 380 mg (as HCl), LOU 4

Indications and dose

Adult

Treatment against alcoholism to reduce the risk of relapse, as support treatment in abstinence and to reduce the craving for alcohol, oral: 50 mg once daily. may increase to 100 mg once daily after 1 week based on response and tolerability.

Treatment against alcoholism to reduce the risk of relapse, as support treatment in abstinence and to reduce the craving for alcohol, IM: 380 mg once every 4 weeks.

Opioid use (mild to moderate), Oral: Initial: 25 mg once daily for 1 to 3 days, if no withdrawal signs occur, administer 50 mg once daily thereafter.

Opioid use (mild to moderate), IM: 380 mg once every 4 weeks.

Paediatric: Safety and efficacy in medically assisted therapy clinics for paediatrics not established

Contraindication: patients currently dependent on opioids, Hepatic impairment, renal impairment, Pregnancy, Breastfeeding

Hepatic impairment: Dose adjustment not necessary.

Renal impairment: Use with caution.

Use in pregnancy/breastfeeding: Contraindicated

Adverse effects: nervousness, anxiety, insomnia, headache, restlessness, abdominal pain, nausea, emesis, rash, asthenia

Interaction with other medicines: opiate derivatives, methyl dopa

Note:

» Use only for patients who are highly motivated or able to comply with techniques such as observed dosing to enhance adherence.

» Naltrexone implant 765 mg is availed on specialist request only.

Nicotine Replacement Therapy

ATC code: N07BA01

Chewing gum, 2 mg, 4 mg, LOU

Transdermal patch, 7–21 mg/24 hours, LOU 4

Indications and dose

Adult

Smoking cessation, Gum, oral: Weeks 1 to 6: Chew 1 piece of gum every 1 to 2 hours (maximum: 24 pieces/day), to increase chances of quitting, chew at least 9 pieces/day during the first 6 weeks. Weeks 7 to 9: Chew 1 piece of gum every 2 to 4 hours (maximum: 24 pieces/day). Weeks 10 to 12: Chew 1 piece of gum every 4 to 8 hours (maximum: 24 pieces/day).

Patients smoking >10 cigarettes/day: Begin with step 1 (21 mg/day) for 6 weeks, **followed by** step 2 (14 mg/day) for 2 weeks, **finish with** step 3 (7 mg/day) for 2 weeks.

Patients smoking ≤10 cigarettes/day: Begin with step 2 (14 mg/day) for 6 weeks, **followed by** step 3 (7 mg/day) for 2 weeks.

Smoking cessation, By transdermal application using patches:

Individuals who smoke more than 10 cigarettes daily should apply a high-strength patch daily for 6–8 weeks, followed by the medium-strength patch for 2 weeks, and then the low-strength patch for the final 2 weeks, individuals who smoke fewer than 10 cigarettes daily can usually start with the medium strength patch for 6–8 weeks, followed by the low strength patch for 2–4 weeks.

Paediatric: Safety and efficacy not established

Contraindication: Hypersensitivity to nicotine or any component of the product

Hypersensitivity to menthol

Precautions: Diabetes mellitus—blood-glucose concentration should be monitored closely when initiating treatment, hemodynamically unstable patients hospitalised with cerebrovascular accident, hemodynamically unstable patients hospitalised with MI, hemodynamically unstable patients hospitalised with severe arrhythmias, phaeochromocytoma, uncontrolled hyperthyroidism

Use in pregnancy/breastfeeding: After the sixth month of pregnancy, the lozenge should only be used under medical supervision in pregnant smokers who have failed to stop smoking by the third trimester. Avoid in breastfeeding if possible.

Hepatic impairment: Dose adjustment not necessary.

Renal impairment: Dose adjustment not necessary.

Pregnancy: Use of nicotine replacement therapy is preferable to continuing smoking.

Breastfeeding: Compatible with breastfeeding.

Adverse effects: dizziness, headache, nausea, flatulence, hiccups, gastritis, dry mouth, stomatitis and oesophagitis

Interaction with other medicines: Adenosine, cimetidine

25.6. Medicines Used In Attention Deficit Hyperactivity Disorder (ADHD)

Atomoxetine

ATC code: N06BA09

Tablets, 10 mg, LOU 6

Indications and dose

Adult

Attention deficit hyperactivity disorder (initiated by a specialist), oral:

Body weight up to 70 kg: Initially 500 micrograms/kg daily for 7 days, dose is increased according to response; maintenance 1.2 mg/kg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 1.8 mg/kg per day; maximum 100 mg per day

Body weight ≥70 kg: Initially 40 mg daily for 7 days, dose is increased according to response; maintenance 80–100 mg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 100 mg per day

Paediatric

Attention deficit hyperactivity disorder (initiated by a specialist), oral:

Child 6–17 years (body weight up to 70 kg): Initially 500 micrograms/kg daily for 7 days, dose is increased according to response; maintenance 1.2 mg/kg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 1.8 mg/kg per day; maximum 100 mg per day

Child 6–17 years (body weight ≥ 70 kg): Initially 40 mg daily for 7 days, dose is increased according to response; maintenance 80 mg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 100 mg per day.

Contraindications: Phaeochromocytoma, severe cardiovascular disease, severe cerebrovascular disease

Precautions: Aggressive behavior, cardiovascular disease, cerebrovascular disease, emotional lability, history of seizures, hostility, hypertension, mania, psychosis, QT-interval prolongation, structural cardiac abnormalities, susceptibility to angle-closure glaucoma, tachycardia.

Hepatic impairment: Manufacturer advises halve dose in moderate impairment and quarter dose in severe impairment.

Renal impairment: No dosage adjustment is necessary.

Pregnancy: Manufacturer advises avoid unless potential benefit outweighs risk.

Breastfeeding: Avoid- present in milk in animal studies.

Adverse effects: Common or very common: anxiety, decreased appetite, arrhythmias (uncommon in children), asthenia, chills, constipation, depression, dizziness, drowsiness, dry mouth, feeling jittery, flatulence, gastrointestinal discomfort, genital pain (rare in children), headaches, hyperhidrosis (uncommon in children), menstrual cycle irregularities, altered mood, mydriasis (in children), nausea, palpitations (uncommon in children), prostatitis (in adults), abnormal sensation (uncommon in children), sexual dysfunction (rare in children), skin reactions, sleep disorders, altered taste, thirst, tremor (uncommon in children), urinary disorders (rare in children), vasodilation, vomiting and decreased weight. Uncommon: abnormal behavior, chest pain (very common in children), dyspnoea, feeling cold, hypersensitivity, muscle spasms, peripheral coldness, QT interval prolongation, suicidal behavior, syncope, tic (very common in children), blurred vision. Rare or very rare: Hallucination (uncommon in children), hepatic disorders, psychosis (uncommon in children), Raynaud's phenomenon, seizure (uncommon in children). Frequency not known: Sudden cardiac death.

Interactions with other medicines (*indicates serious): * MAOIs– avoid and for 2 weeks after stopping the MAOI, CYP2D6 inhibitors (*SSRIs) – adjust dose, beta2 agonists (high dose), antihypertensives, * terbinafine- adjust dose, *Panobinostat - monitor and adjust dose, givosiran, fedratinib, eliglustat, berotralstat, *amfetamines, *bupropion, *cinacalcet, *dacomitinib, eligustat.

Notes: The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated. Despite higher doses having been used, doses above 100mg daily are unlicensed.

Methylphenidate

ATC code: N06BA04

Tablet, 10 mg, LOU 4

Tablet (e/r), 18mg (LOU 4), 27mg (LOU 5)

Indications and dose

Adult

Attention-Deficit Hyperactivity Disorder, Oral (immediate release tablet): Initially 5 mg once daily or twice daily (e.g., at breakfast and lunch), increasing if necessary by weekly increments of 5–10 mg in the daily dose according to tolerability and degree of efficacy observed to a maximum of 100 mg per day. If effect wears off in the evening, a bedtime dose may be appropriate.

Attention-Deficit Hyperactivity Disorder, Oral (extended-release): Initially 18 mg once daily, dose to be taken in the morning, adjusted at weekly intervals according to response, maximum 108 mg per day.

Paediatric

Attention-Deficit Hyperactivity Disorder, Oral (immediate release tablet):

Child 6–17 years: Initially 5 mg 1–2 times a day, increased in steps of 5–10 mg daily if required, at weekly intervals, increased if necessary up to 60 mg daily in 2–3 divided doses, increased if necessary up to 2.1 mg/kg daily in 2–3 divided doses, the licensed maximum dose is 60 mg daily in 2–3 doses, higher dose (up to a maximum of 90 mg daily) under the direction of a specialist, discontinue if no response after 1 month, if effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate.

Attention-Deficit Hyperactivity Disorder, Oral (extended-release):

Child 6–17 years: Initially 18 mg once daily, dose to be taken in the morning, increased in steps of 18 mg every week, adjusted according to response, increased if necessary up to 2.1 mg/kg daily, max. dose is 54 mg once daily, to be increased to higher dose only under direction of specialist, discontinue if no response after 1 month, maximum 108 mg per day.

Contraindication: Absolute-history of schizophrenia, drug dependence or personality disorders, patients with glaucoma, thyrotoxicosis, tachyarrhythmias, anxiety, tension or ischaemic heart disease.

Precautions: Use strictly controlled and actively monitored. Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate.

Hepatic impairment: Dose adjustment not necessary

Renal impairment: Dose adjustment not necessary

Use in pregnancy/breastfeeding: avoid if possible.

Adverse effects: Nasopharyngitis, insomnia, nervousness, headache, arrhythmia, cough

Interaction with other medicines:

barbiturates, primidone, phenytoin, phenyl butazone, tricylic antidepressants, warfarin, and MAO inhibitors (rasagiline, selegiline), linezolid, paliperidone, risperidone

25.7. Medicines For Sleep Disorders

Melatonin

ATC code: N05CH01

Tablet (soluble), 3mg, 4mg, LOU 2

Indications and dose

Adult

Insomnia, oral: 3 – 5mg at bedtime

Difficulty falling asleep, oral: 5mg 3 – 4 hours before sleep period for 4 weeks

Paediatric

Not recommended

Contraindication: Concurrent immunosuppressive treatment

Precautions: Autoimmune disease (manufacturer advises avoid—no information available)

Hepatic impairment: consider dose reduction in moderate hepatic disorders associated with alcoholism.

Renal impairment: Increased cerebral sensitivity. Start with small doses in severe impairment.

Pregnancy: Avoid

Breastfeeding: Use only if benefit outweighs risk

Adverse effects: Abdominal cramps, Alertness decreased, Circadian rhythm disruption, daytime fatigue, Depression (transient), Dizziness, Drowsiness, Dysphoria in depressed patients, Headache, Irritability

Interaction with other medicines: Abametapir, Fluvoxamine, Warfarin

Zolpidem

ATC code: N05CF02

Tablet, 10 mg, LOU 4

Indications and dose

Adult

Insomnia (short-term use), oral: 10 mg daily for up to 4 weeks, dose to be taken at bedtime, for debilitated patients, use elderly dose

» Elderly: 5 mg daily for up to 4 weeks, dose to be taken at bedtime

Paediatric

Insomnia (short-term use), oral:

Children and adolescents ≤17 years: 0.25 mg/kg at bedtime, maximum dose 10 mg/dose

Contraindication: Patients with known hypersensitivity to zolpidem, observed reactions include anaphylaxis and angioedema

Patients who have experienced complex sleep behaviors after receiving therapy

Acute respiratory depression, marked neuromuscular respiratory weakness, obstructive sleep apnoea, psychotic illness, severe respiratory depression, unstable myasthenia gravis

Precautions: Avoid prolonged use (and abrupt withdrawal thereafter), depression, elderly, history of alcohol abuse, history of drug abuse, muscle weakness, myasthenia gravis

Hepatic impairment: Avoid in severe impairment

Renal impairment: Use with caution

Pregnancy: Avoid regular use (risk of neonatal withdrawal symptoms), high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression

Breastfeeding: Present in breast milk. Avoid

Adverse effects: Dizziness, Headache, Drowsiness, Allergy, Hallucinations, Myalgia, Sinusitis, Memory disorder, Visual disturbance, Pharyngitis, Lightheadedness, Palpitation, Rash, Constipation, Depression, Drowsiness, Asthenia, Diarrhea, Dry mouth, Flu-like symptoms, Respiratory depression, Complex sleep behaviors

Interaction with other medicines:(*Indicates Serious)

Darunavir, azelastine, bromperidol, *thalidomide, opioid analgesics, minocycline, tocilizumab, melatonin, CNS depressants.

26.Medicines Acting On the Respiratory Tract

26.1. Antiasthmatic Medicines & Medicines For Chronic Obstructive Pulmonary Disease

Budesonide

ATC code: R03BA02

Inhalation (aerosol), 100 micrograms per dose, 200 micrograms per dose, LOU 4

Indications and dose

Adult

Prophylaxis of mild to moderate asthma, inhalation: 200–400 micrograms once daily (max. per dose 800 micrograms), dose to be given in the evening

Paediatric

Prophylaxis of asthma, inhalation (aerosol)

Child 6–11 years: 200–400 micrograms once daily, dose to be given in the evening

Child 12–17 years: 200–400 micrograms once daily (max. per dose 800 micrograms), dose to be given in the evening

Broncho pulmonary dysplasia, inhalation

Child and neonate, 1–4 months: 400 micrograms every 12 hours

Precautions: Systemic corticosteroid therapy may be required during periods of stress, such as severe infections or when airways obstruction or mucus prevent drug access to smaller airways.

Adverse effects: Common Dysphonia (hoarse voice), oropharyngeal candidiasis (risk reduced by using a spacer device, rinsing the mouth with water or cleaning the child's teeth after inhalation), bruising.

Rare Allergic reactions, including bronchospasm, rash, urticaria and angioedema.

Occurrence of systemic adverse effects is dose dependent.

Interaction with other medicines:

Interactions listed relate to systemically absorbed drug, consider relevance when using inhaled drug.

Ritonavir: ritonavir inhibits CyP3A4 and as such may increase the concentration of budesonide by inhibiting its metabolism. Cases of Cushing syndrome reported with concurrent use of fluticasone and ritonavir.

Budesonide + Formoterol

ATC code: R03AK07

Metered dose inhalers, 100micrograms + 6 micrograms per metered dose, 200micrograms + 6micrograms per metered dose, LOU 4

Dry powder inhaler, 80micrograms + 4.5micrograms per metered dose, 160micrograms + 4.5micrograms per metered dose, LOU 4

Indications and dose

Adult

Asthma patients requiring step-up from inhaled corticosteroid monotherapy: 1 to 2 inhalations twice daily until symptom control, then titrate to lowest effective dosage to maintain control

Paediatric

Child<6 years: Safety and efficacy not established

Child 6-12 years: 2 inhalations twice daily until symptom control, then titrate to lowest effective dosage to maintain control

Child>12 years: Starting dose is based on asthma severity

1 to 2 inhalations twice daily until symptom control, then titrate to lowest effective dosage to maintain control; not to exceed 4 inhalations every 12 hours.

If response is inadequate after 1-2 weeks of therapy with 80 mcg/4.5 mcg, switching to 160 mcg/4.5 mcg may provide additional control

Contraindication: Status asthmaticus, acute episodes of asthma.

Precautions: Use in pregnancy/breastfeeding: limited data. Weigh benefits to mother against risk to child

Adverse effects: Body aches or pain, chills, cough, difficulty with breathing ear congestion, fever, headache, loss of voice, muscle aches, pain or tenderness around the eyes and cheekbones, sneezing, sore throat, stuffy or runny nose, tightness of the chest, unusual tiredness or weakness

Interaction with other medicines:

Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Amphotericin B and adverse effects of beta agonists.

Epinephrine (Adrenaline)

ATC code: C01CA24

Injection, 1 mg (as HCl or hydrogen tartrate) in 1-mL amp, LOU 2

Indications and dose

Adult

Acute asthma, as rescue therapy when B2 agonist not available or no response to maximal B2 agonist doses, SC:500micrograms (0.5ml of 1:1000); dose may be repeated every 5 minutes according to blood pressure, pulse and respiratory function.

Paediatric

Acute asthma, SC

Child all ages: 0.01 mL/kg of 1:1000 solution up to a maximum of 0.5 mL; may repeat every 20 minutes for up to three doses

Contraindications: Hypertension, cardiac arrhythmias, closed-angle glaucoma, psychoneurosis, use during

halothane or cyclopropane anaesthesia.

Precautions: Hyperthyroidism, diabetes mellitus, heart disease, cerebrovascular disease, phaeochromocytoma, susceptibility to closed-angle glaucoma.

arrhythmias, second stage of labour and the elderly.

Hepatic Impairment: No dose reduction needed.

Renal Impairment: No dose reduction needed.

Adverse effects: Common: Nausea, vomiting, anxiety, headache, fear, palpitations, tachycardia, restlessness, tremor, dizziness, dyspnoea, weakness, sweating, pallor, hyperglycaemia. Excessive increase in blood pressure, ventricular arrhythmias, pulmonary oedema (on excessive dosage or extreme sensitivity), angina, cold extremities, peripheral ischaemia and necrosis (at infusion site).

Rare: Allergic reaction (sodium metabisulfite in some products).

Overdose or rapid IV administration arrhythmias (ventricular and supraventricular), severe hypertension, cerebral haemorrhage, pulmonary oedema.

Interaction with other medicines (*indicates serious):

Amitriptyline: increased effect or toxicity of epinephrine.

* Cyclopropane: may precipitate ventricular arrhythmias.

* Ergot derivatives: may precipitate hypertensive crisis.

Fluoxetine: increased effect or toxicity of epinephrine.

* Halothane: may precipitate ventricular arrhythmias.

Propranolol: hypertension, bradycardia, resistance to epinephrine effect.

Severe anaphylaxis in patients on non-cardio selective beta- blockers, for example propranolol, may not respond to epinephrine (adrenaline) injection calling for IV injection of salbutamol. Furthermore, epinephrine (adrenaline) may cause severe hypertension in those receiving beta-blockers. Patients on tricyclic antidepressants are considerably more susceptible to arrhythmias, calling for a much reduced dose of epinephrine.

Notes:

- 1 mg/mL = 1:1000 or 0.1%.
- Different dilutions of epinephrine injection are used for different routes of administration.
- IV epinephrine should be used with extreme care by specialists only.

Ipratropium bromide

ATC code: R03BB01

Inhalation (aerosol), 20 micrograms/metered dose (200 dose), LOU 4

Nebuliser solution, 500 micrograms/2 mL unit dose vial (isotonic), LOU 4

Indications and dose

Adult

Chronic asthma, chronic obstructive pulmonary disease, by aerosol inhalation: 20–40 micrograms, 3–4 times daily

Chronic obstructive pulmonary disease, by inhalation of nebulized solution: 250–500 micrograms 3–4 times daily

Adjunct in acute bronchospasm, by inhalation of nebulized solution: 500 micrograms repeated as required

Paediatric

Chronic asthma, chronic obstructive pulmonary disease, by aerosol inhalation

Child up to 6 years: 20 micrograms 3 times daily

Child 6–12 years: 20–40 micrograms 3 times daily

Adjunct in acute bronchospasm, by inhalation of nebulized solution

Child up to 6 years: 125–250 micrograms, maximum 1 mg daily

Child 6–12 years: 250 micrograms, maximum 1 mg daily

Contraindications: closed angle glaucoma, blockage of the urinary bladder, enlarged prostate, an inability to completely empty the bladder

Precautions: prostatic hypertrophy, glaucoma (standard doses unlikely to be harmful but reported with nebulized drug, particularly in association with nebulized salbutamol, care needed to protect patient's eyes from drug powder or nebulized drug), medical supervision necessary for first dose of nebulized solution (risk of paradoxical bronchospasm).

Adverse effects: occasionally dry mouth, rarely urinary retention and constipation, tachycardia and atrial fibrillation also reported.

Interaction with other medicines:

Severe interaction are for Pramlintide, Some minor interactions are for dimenhydrinate, donepezil, galantamine, levodopa and tacrine, anticholinergics.

Montelukast

ATC code: R03DC03

Tablet (chewable), 5 mg (as sodium salt), LOU 4

Tablet, 10 mg (as sodium salt), LOU 4

Indications and dose

Adult

Prophylaxis of asthma, oral: 10 mg once daily, to be taken in the evening

Symptomatic relief of seasonal allergic rhinitis in patients with asthma, oral: 10 mg once daily, dose to be taken in the evening

Paediatric

Prophylaxis of asthma, oral

Child 6 months–5 years: 4 mg once daily, dose to be taken in the evening

Child 6–14 years: 5 mg once daily, to be taken in the evening

Child 15–17 years: 10 mg once daily, to be taken in the evening

Symptomatic relief of seasonal allergic rhinitis in patients with asthma, oral

Child 15–17 years: 10 mg once daily, to be taken in the evening

Precautions: Neuropsychiatric reactions, including speech impairment and obsessive-compulsive symptoms, in adults, adolescents, and children taking montelukast; Evaluate the risks and benefits of continuing treatment if these reactions occur.

Pregnancy: Manufacturer advises avoid unless essential. There is limited evidence for the safe use of montelukast during pregnancy, however, it can be taken as normal in women who have shown a significant improvement in asthma not achievable with other drugs before becoming pregnant.

Breastfeeding avoid unless essential.

Adverse effects: Abdominal pain and disturbances, thirst, hyperkinesia (in young children), headache, dry mouth, diarrhoea, dyspepsia, nausea, vomiting, hepatic disorders, palpitation, oedema, increased bleeding, hypersensitivity reactions (including anaphylaxis and skin reactions), depression, suicidal thoughts and psychiatric behaviour, tremor, asthenia, dizziness, hallucinations, paraesthesia, hypoaesthesia, sleep disturbances, abnormal dreams, agitation, aggression, seizures, arthralgia and myalgia, Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) has occurred very rarely in association with the use of montelukast, in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy.

Prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.

Interaction with other medicines: Fluticasone/salmeterol, Aspirin, Aspirin Low Strength, Diphenhydramine, Fluticasone/vilanterol Duloxetine, Fish Oil (omega-3 polyunsaturated fatty acids), Fluticasone nasal

Salbutamol

ATC code: R03CC02

Nebuliser solution, 5 mg/mL (as sulphate), LOU 2

Indications and dose

Adult

Severe acute asthma, chronic bronchospasm (unresponsive to conventional treatment), by inhalation of nebulized solution: 2.5 mg repeated up to 4 times daily, may be increased to 5 mg if necessary (medical assessment should be considered because alternative therapy may be indicated)

Paediatric

Moderate, severe, or life-threatening acute asthma, by inhalation of nebulised solution

Child 1 month–4 years: 2.5 mg, repeat every 20–30 minutes or when required; give via oxygen-driven nebuliser if available

Child 5–11 years: 2.5–5 mg, repeat every 20–30 minutes or when required; give via oxygen-driven nebuliser if available

Child 12–17 years: 5 mg, repeat every 20–30 minutes or when required; give via oxygen-driven nebuliser if available

Contraindications: Patients who are hypersensitive to salbutamol or its excipients, Patients who are on non-selective beta blocking drugs such as Propranolol and Cardiac glycosides.

Precautions: hyperthyroidism, myocardial insufficiency, arrhythmias, susceptibility to QT-interval prolongation, hypertension, pregnancy (high doses should be given by inhalation because parenteral use can affect the myometrium and possibly cause cardiac problems, diabetes mellitus, especially IV administration (ketoacidosis reported, monitor blood glucose),

Interaction with other medicines:

(Interactions may not be experienced with inhalational salbutamol)

Acetazolamide: Increased risk of hypokalaemia with high doses of salbutamol.

Dexamethasone: Increased risk of hypokalaemia if high doses of salbutamol given with dexamethasone.

Digoxin: Possibly reduced plasma concentration of digoxin.

Furosemide: Increased risk of hypokalaemia with high doses of salbutamol.

Hydrochlorothiazide- Increased risk of hypokalaemia with high doses of salbutamol.

Hydrocortisone: Increased risk of hypokalaemia if high doses of salbutamol given with hydrocortisone.

Methyldopa: Acute hypotension reported with salbutamol infusion

Prednisolone: Increased risk of hypokalaemia if high doses of salbutamol given with prednisolone

Salbutamol + Beclomethasone

ATC code: N/A

Inhalation (aerosol), 100 micrograms + 50 micrograms, LOU 3

Indications and dose

Adult

Management of exacerbation of asthma: Two inhalations, three or four times daily, titrated to the lowest effective dose

Paediatric

Management of exacerbation of asthma: Two inhalations, three or four times daily, titrated to the lowest effective dose

Contraindications: Hypersensitivity to any of the components of the formulation. Beclomethasone is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. Special care is necessary with the use of beclomethasone dipropionate in patients with active or quiescent pulmonary TB.

Precautions: Salbutamol may cause paradoxical bronchospasm, which may be life threatening. If it occurs, should be discontinued immediately.

Adverse effects: pain, dizziness, asthma, pharyngitis, and rhinitis whereas those observed in children were vomiting, bronchitis and pharyngitis, less than 2%

were cyst, flu syndrome, viral infection, constipation, gastroenteritis, myalgia, hypertension, epistaxis, lung disorder, acne, herpes simplex, conjunctivitis, ear pain, dysmenorrhea, hematuria, and vaginal moniliasis. In children, frequently occurring adverse events were accidental injury, vomiting, bronchitis, pharyngitis.

Salbutamol + Ipratropium

ATC code: R03AL02

Salbutamol (as sulphate) 2.5mg + ipratropium (as bromide) 500micrograms in 2.5mL amp, LOU 3

Indications and dose

Adult

Bronchospasm in chronic obstructive pulmonary disease, by inhalation of nebulised solution: 1 ampoule 3–4 times a day

Paediatric

Adjunct in acute bronchospasm, by inhalation of nebulized solution:

Child over 12 years: 1 ampoule 3–4 times a day

Contraindications:

For Ipratropium it is contraindicated in patients with closed angle glaucoma., blockage of the urinary bladder., enlarged prostate and those with inability to completely empty the bladder.

For Salbutamol see under (Salbutamol nebulizing solution)

Interaction with other medicines: *see separately under Ipratropium and salbutamol*

Notes:

» Prescribing and dispensing information: A mixture of ipratropium bromide and salbutamol (as sulphate), the proportions are expressed in the form x/y where x and y are the strengths of ipratropium and salbutamol respectively.

Tiotropium

ATC code: R03BB04

Powder for inhalation in a capsule, 18 micrograms/capsule, LOU 4

Metered dose inhaler (inhalation solution), 2.5 micrograms per actuation, LOU 4

Indications and dose

Adult

Maintenance treatment of chronic obstructive pulmonary disease, by inhalation (using powder for inhalation 18 microgram/capsule): 1 capsule once daily

Maintenance treatment of chronic obstructive pulmonary disease, severe asthma (add-on to inhaled corticosteroid [at least 800 micrograms budesonide daily or equivalent] and at least 1 controller in patients who have suffered one or more severe exacerbations in the last year), by inhalation (using solution for inhalation 2.5microgram/ dose device): 5 micrograms (2 puffs) once daily.

Paediatric

Children and adolescents below 18years:

Tiotropium 18 micrograms is not recommended.

Severe asthma [add-on to inhaled corticosteroid (over 400 micrograms budesonide daily or equivalent) and 1 controller, or inhaled corticosteroid (200–400 micrograms budesonide daily or equivalent) and 2 controllers, in patients who have suffered one or more severe exacerbations in the last year], by inhalation (using solution for inhalation 2.5 microgram/dose device):

Child 6–11 years: 5 micrograms (2 puffs) once daily

Severe asthma [add-on to inhaled corticosteroid (over 800 micrograms budesonide daily or equivalent) and 1 controller, or inhaled corticosteroid (400–800 micrograms budesonide daily or equivalent) and 2 controllers, in patients who have suffered one or more severe exacerbations in the last year], by inhalation (using solution for inhalation 2.5 microgram/dose device):

Child 12–17 years: 5 micrograms (2 puffs) once daily

Precautions: Bladder outflow obstruction, paradoxical bronchospasm, prostatic hyperplasia, susceptibility to angle-closure glaucoma, Arrhythmia (unstable, life-threatening or requiring intervention in the previous 12 months).

Heart failure (hospitalisation for moderate to severe heart failure in the previous 12 months), MI in the previous 6 months.

Renal impairment- Manufacturer advises use only if potential benefit outweighs risk if CrCl less than or equal to 50 mL/min—plasma-tiotropium concentration raised.

Pregnancy -Manufacturer advises avoid - limited data available.

Breastfeeding- Manufacturer advises avoid - no information available.

Adverse effects: common: dry mouth

uncommon: dizziness, headache, taste disorders, blurred vision, irregular heartbeat (artrial fibrillation), inflammation of the throat (pharyngitis), hoarseness (dysphonia), cough, GERD, constipation, oropharyngeal candidiasis, rash, urinary retention, dysuria.

Rare: insomnia, glaucoma, increase in measured eye pressure, supraventricular tachycardia, tachycardia, palpitations, bronchospasm, epistatxis, laryngitis, sinusitis, intestinal obstruction including ileus paralytic, gingivitis, glossitis, dysphagia, stomatitis, nausea, hypersensitivity reactions, angioedema, urticaria, pruritus, infections of urinary tract.

Interaction with other medicines: Serious interaction of Tiotropium include pramlintide, Minor interaction of Tiotropium include dimenhydrinate, donepezil, galantamine and tacrine.

Notes: Patient and caregiver advice: Should be given advice on appropriate inhaler technique and reminded that the powder inhalation capsules are not for oral administration.

26.2. Medicines For Idiopathic Pulmonary Fibrosis

Nintedanib

ATC code: L01EX09

Capsule, 150 mg, LOU 6

Indications and dose

Adult

Treatment of progressive fibrotic lung diseases including systemic sclerosis related interstitial lung disease (ILD), Oral: 150 mg every 12 hours

Paediatric

Safety and efficacy in children not established

Contraindications:

Pregnancy

Hypersensitivity to nintedanib, to peanut or soya, or to any of the excipients.

Precautions: In case of persisting severe diarrhoea, nausea or vomiting despite symptomatic treatment, therapy with nintedanib should be discontinued.

Hepatic impairment: Reduce the dose in patients with mild hepatic impairment. Use in patients with moderate and severe hepatic impairment not recommended.

Renal impairment: Monitor the patient and adjust the dosage as necessary.

Breastfeeding: Discontinue breastfeeding during therapy

Adverse effects: diarrhoea, nausea and vomiting, abdominal pain, decreased appetite, weight decreased, hepatic enzyme increased.

Interactions with other medicines:

Potent P-gp inhibitors (e.g., ketoconazole, erythromycin or cyclosporine) may increase exposure to nintedanib.

Potent P-gp inducers (e.g., rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib

Pirfenidone

ATC code: L04AX05

Tablets, 267mg, LOU 5

Indications and dose

Adult

Treatment of mild to moderate idiopathic pulmonary fibrosis (initiated under specialist supervision), oral: Initially 267 mg three times a day for 7 days, then increased to 534 mg three times a day for 7 days, then increased to 801 mg three times a day. Taken with food.

Paediatric: Limited data available.

Contraindications: Severe hepatic and renal impairment

Precautions: Manufacturer advises avoid exposure to direct sunlight—if photosensitivity reaction or rash occurs, dose adjustment or treatment interruption may be required.

Hepatic impairment: Manufacturer advises caution in mild to moderate impairment (risk of increased exposure); avoid in severe impairment (no information available).

Renal impairment: Caution if creatinine clearance 30–50 mL/minute; avoid if creatinine clearance less than 30 mL/minute.

Pregnancy: Manufacturer advises avoid—no information available.

Breastfeeding: Manufacturer advises avoid—no information available.

Adverse effects: Common or very common: decreased appetite, arthralgia, asthenia, constipation, diarrhoea, dizziness, drowsiness, gastrointestinal discomfort, gastrointestinal disorders, headache, hot flush, increased risk of infection, insomnia, musculoskeletal chest pain, myalgia, nausea, photosensitivity reaction, productive cough, skin reactions, sunburn, altered taste, vomiting, decreased weight. Uncommon: Agranulocytosis, angioedema, hepatic disorders, hyponatraemia. Frequency not known: Severe cutaneous adverse reactions (SCARs)

Interactions with other medicines: Concomitant use with ciprofloxacin— reduce dose of pirfenidone to 534 mg three times daily with high-dose ciprofloxacin (750 mg twice daily). Patients also taking inhibitors of cytochrome P450 isoenzymes involved in the metabolism of pirfenidone should be closely monitored for toxicity.

Notes:

» If treatment is interrupted for 14 consecutive days or more, the initial 2 week titration regimen should be repeated; if

27. Ear, Nose & Throat Medicines

27.1. Medicines For the Ear

Benzocaine + Chlorbutol + Paradichlorobenzene + Turpentine oil

ATC code: S02DC

Solution (ear drops), 2.7%+2%+5%+15%, 10mL, LOU 3

Indications and dose

Adult

Used to dissolve earwax and relieve ear discomfort, aurally: **10 drops per ear; sufficient to fill the affected ear.**

Paediatric:

As for adult dose only if recommended by a doctor

Precautions: Allergy to any of the ingredients of the product. Avoid contact of product with eyes, nose, or mouth. In case of accidental contact with these areas, rinse with water thoroughly. If you experience ear discharge, drainage, worsening pain, or any signs of skin rash, stop using the product and seek. Do not apply for more than 2 consecutive nights.

Pregnancy & Breastfeeding: No data, use with caution.

Adverse effects: Headache, Sleeplessness

Notes:

» Method of administration: Apply before going to bed, tilt the head and fill the ear canal with the Ear Drops. Plug the ear using cotton wool, leaving in the ear overnight. The softened earwax should come out of the ear without requiring syringing.

Betahistine

ATC code: N07CA01

Tablet, 8mg, 16mg, LOU 5

Indications and dose

Adult

Vertigo, tinnitus, and hearing loss associated with Ménière's disease, oral: Initially 8-16 mg three times a day, dose preferably taken with food; maintenance 24–48 mg daily in divided doses.

Paediatric: Not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Patients with phaeochromocytoma. As betahistine is a synthetic analogue of histamine it may induce the release of catecholamines from the tumor resulting in severe hypertension.

Precautions: Asthma, history peptic ulcer, severe hypotension.

Pregnancy: Avoid unless clearly necessary -no information available.

Breastfeeding: Use only if potential benefit outweighs risk - no information available.

Adverse effects: Common or very common: Gastrointestinal discomfort, headache, nausea. Frequency not known: Allergic dermatitis, vomiting.

Interactions with other medicines (*indicates serious): Sedating anti-histamines decrease effects of betahistine.

Cinnarizine

ATC code: N07CA02

Tablets, 25 mg, LOU 5

Indications and dose

Adult

Relief of symptoms of vestibular disorders, such as vertigo, tinnitus, nausea, and vomiting in Ménière's disease, oral: 30 mg 3 times a day

Motion sickness, oral: Initially 30 mg, dose to be taken 2 hours before travel, then 15 mg every 8 hours if required, dose to be taken during journey

Paediatric

Relief of symptoms of vestibular disorders, such as vertigo, tinnitus, nausea, and vomiting in Ménière's disease, oral

Child 5–11 years: 15 mg 3 times a day

Child 12–17 years: 30 mg 3 times a day

Motion sickness, oral

Child 5–11 years: Initially 15 mg, dose to be taken 2 hours before travel, then 7.5 mg every 8 hours if required, dose to be taken during journey

Child 12–17 years: Initially 30 mg, dose to be taken 2 hours before travel, then 15 mg every 8 hours if required, dose to be taken during journey

Contraindications: Avoid in Acute porphyrias

Precautions: Epilepsy, glaucoma (in children), Parkinson's disease (in adults), prostatic hypertrophy (in adults), pyloroduodenal obstruction, susceptibility to angle closure glaucoma (in adults), urinary retention

Hepatic impairment Manufacturer advises caution in hepatic insufficiency—no information available.

Renal impairment Use with caution—no information available.

Patient and caregiver advice Driving and skilled tasks: Drowsiness may affect performance of skilled tasks (e.g., cycling, driving), sedating effects enhanced by alcohol.

Pregnancy: Manufacturer advises avoid, however, there is no evidence of teratogenicity. The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

Breastfeeding: Most antihistamines are present in breast milk in varying amounts, although not known to

be harmful, most manufacturers advise avoiding their use in mothers who are breastfeeding.

Adverse effects: Drowsiness, GI discomfort, nausea, weight increased, Fatigue. hyperhidrosis, vomiting, Frequency not known Dry mouth, GI disorder, headache, jaundice cholestatic, movement disorders, muscle rigidity, parkinsonism, skin reactions, subacute cutaneous lupus erythematosus, tremor

Interaction with other medicines: *See Chlorpheniramine*

Ciprofloxacin

ATC code: S02AA15

Topical, 0.3% drops, LOU 2

Indications and dose

Adult

Chronic suppurative otitis media: Apply 5 drops twice daily for 7 days

Paediatric

Chronic suppurative otitis media, topical instillation into ear

Infant or **child:** 5 drops twice daily for 9 days

Contraindications: Hypersensitivity to quinolones including nalidixic acid.

Adverse effects: Common: Local discomfort, bitter taste, fungal infection.

Interaction with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

- To avoid dizziness, which may be associated with instillation of a cold solution into the ear, if the solution is cold, it should be warmed by holding the bottle in the hand for 1 or 2 minutes before instillation.
- Patients or caregivers should be advised to avoid contamination of the dispensing tip.

Ciprofloxacin + Dexamethasone

ATC code: S02CA06

Solution (ear drops), 0.3% (as HCl) + 0.1%, LOU 3

Indications and dose

Adult

Acute otitis media in patients with tympanostomy tubes, to the ear: Apply 4 drops twice daily for 7 days

Acute otitis externa, to the ear: Apply 4 drops twice daily for 7 days

Paediatric

Acute otitis media in patients with tympanostomy tubes, to the ear

Infant or **child:** Apply 4 drops twice daily for 7 days

Acute otitis externa, to the ear

Infant or **child:** Apply 4 drops twice daily for 7 days

Contraindications: Fungal ear infections, viral ear infections

Precautions: Avoid prolonged use; Further evaluation of underlying conditions is advisable if otorrhoea persists after a full course, or if at least two episodes of otorrhoea occur within 6 months.

Adverse effects: Ear discomfort Ear infection fungal, flushing, irritability, malaise, otorrhoea, paraesthesia, skin reactions, taste altered, vomiting, Dizziness, headache, hearing loss, tinnitus

Interactions: Since systemic absorption can follow topical application, the possibility of interactions should be borne in mind according to respective medication class i.e. corticosteroids and quinolones

Notes:

- **Patient and caregiver advice:** Counselling on administration.

Clotrimazole

ATC code: D01AC01

Solution (ear drops) 1%, LOU 3

Indications and dose

Adult

Fungal infections in the ear (otitis externa): 2–3 drops two or three times a day for 14 days

Paediatric

Fungal infections in the ear (otitis externa)

Infant or **child:** 2–3 drops two or three times a day for 14 days

Precautions: If previously had allergic reaction to the medicine

Adverse effects: Burning, irritation, itching and redness immediately after application but will subside without treatment

Interaction with other medicines: Not likely

Hydrogen Peroxide

ATC code: S02AA06

Solution (ear drops), 3% ear drops (stabilized), LOU 2

Indications and dose

Adult

Inflammatory conditions of the external auditory canal and for removal of ear wax: Outer ear (patient should lie down on their side); administer the instructed number of drops into the ear canal and fill it with fluid; keep still for 5 minutes; sit up after 5 minutes and blot the outer ear with a tissue to absorb any liquid that comes out; repeat for the other ear

Paediatric: Follow adult dosing

Adverse effects: Redness, Stinging, Irritation

Note:

This 3% strength is also expressed as '10-volume'. If unavailable, use other available forms and strengths and dilute as required to 3% for use as ear drops

27.2. Medicines For the Nose

Budesonide

ATC code: R01AD05

Nasal spray, 100 micrograms per metered dose, LOU 4

Indications and dose

Adult

Prophylaxis and treatment of allergic and vasomotor rhinitis, by intranasal administration: Initially 200 micrograms once daily, dose to be administered into each nostril in the morning; alternatively initially 100 micrograms twice daily, dose to be administered to each nostril, reduced to 100 micrograms once daily, dose to be administered into each nostril; dose can be reduced when control achieved

Nasal polyps, by intranasal administration: 100 micrograms twice daily for up to 3 months, dose to be administered into each nostril

Paediatric

Prophylaxis and treatment of allergic and vasomotor rhinitis

Child 12–17 years: Initially 200 micrograms once daily, dose to be administered into each nostril in the morning; alternatively, initially 100 micrograms twice daily, dose to be administered to each nostril; reduced to 100 micrograms once daily, dose to be administered into each nostril; dose can be reduced when control achieved

Contraindications: Severe nasal infection.

Precautions: Bleeding disorders as intranasal corticosteroids may cause nose bleeding, recent nasal surgery or trauma as intranasal corticosteroids may delay healing, avoid in pulmonary TB, avoid in the presence of untreated nasal infections, patients transferred from systemic corticosteroids may experience exacerbation of some symptoms

Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged, therefore, also consider the cautions and adverse effects of systemic corticosteroids. The risk of systemic effects may be greater with nasal drops than with nasal sprays, drops are administered incorrectly more often than sprays.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Systemic adverse effects are rare with nasal products used at recommended doses. Nasal stinging, itching, sneezing, sore throat, dry mouth, cough. Nose bleed. Nasal septal perforation, glaucoma, cataract, allergic reactions (urticaria, angioedema, bronchospasm, rash), raised intraocular pressure and other systemic effects

Interaction with other medicines: There are no known interactions where it is recommended to avoid concomitant use.

Notes:

» Onset of action within 3–7 hours, effective on an as-needed basis, optimum effect after several days of regular use. Patients transferred from oral to intranasal corticosteroids may have impaired adrenal function, intranasal corticosteroids have little systemic effect.

» Shake the canister gently before use and prime by actuating eight times prior to initial use. If not used for two consecutive days, re-prime until a fine mist appears. If not used for 14 days, rinse the applicator and re-prime until a fine mist appears.

Fluticasone

ATC code: R03BA05

Nasal spray, 27.5 micrograms (as propionate or furoate), LOU 5

Indications and dose

Adult

Prophylaxis and treatment of allergic rhinitis and perennial rhinitis and nasal polyps

By intranasal administration using nasal spray: 100 micrograms once daily, to be administered into each nostril preferably in the morning, increased if necessary to 100 micrograms twice daily, reduced to 50 micrograms once daily, dose to be administered into each nostril, dose to be reduced when control achieved

Treatment of nasal polyps, By intranasal administration using nasal drops: 200 micrograms 1–2 times a day, to be administered into each nostril, alternative treatment should be considered if no improvement after 4–6 weeks, (200 micrograms is equivalent to approximately 6 drops)

Paediatric

Prophylaxis and treatment of allergic rhinitis and perennial rhinitis, By intranasal administration using nasal spray:

Child 4–11 years: 50 micrograms once daily, to be administered into each nostril preferably in the morning, increased if necessary to 50 micrograms twice daily.

Child 12–17 years: 100 micrograms once daily, to be administered into each nostril preferably in the morning, increased if necessary to 100 micrograms twice daily, reduced to 50 micrograms once daily, dose to be administered into each nostril, dose to be reduced when control achieved

Treatment of nasal polyps, By intranasal administration using nasal spray:

Child 16–17 years: 200 micrograms 1–2 times a day, to be administered into each nostril, alternative treatment should be considered if no improvement after 4–6 weeks, (200 micrograms is equivalent to approximately 6 drops)

Adverse effects: Adrenal suppression, Nasal ulceration occurs commonly with nasal preparations containing fluticasone furoate

Interaction with other medicines: As for corticosteroids

Note:

» Check dose equivalents for different brands as well as dosing instructions

Liquid Paraffin

ATC code: A06AA01

Nasal drops,Liquid paraffin 100%, 20 mL LOU 2

Indications and dose

Adult

Relief of congestion in the nose; packing in epistaxis (off label), By installation as nasal drops: Use when necessary

Paediatric

Relief of congestion in the nose; packing in epistaxis (off label), By installation as nasal drops:

Child all ages: Use when necessary

Contraindication/Precautions: Hypersensitivity

Adverse effects: Irritation

Neomycin + Betamethasone

Solution (nasal drops), 0.5% (as sulphate) + (0.1% as sodium phosphate), LOU 4

Indications and dose

Adult

Nasal infection, intranasally: Apply 2–3 drops to each nostril 2–3 times a day

Paediatric

Nasal infection, intranasally:

Child all ages: Apply 2–3 drops to each nostril 2–3 times a day

Contraindications: Patent grommet

Precautions: Avoid prolonged use

Interaction with other medicines: corticosteroids, neomycin

Sodium Chloride

ATC code: A12CA01

Nasal drops 0.9%, LOU 2

Indication and dose

Adult

Dryness inside the nose (nasal passages), helps to add moisture inside the nose to dissolve and soften thick or crusty mucus, by instillation as nasal drops: Apply as required

Paediatric

Dryness inside the nose (nasal passages), helps to add moisture inside the nose to dissolve and soften thick or crusty mucus, by instillation as nasal drops: Apply as required

Contraindication/Precautions: Hypersensitivity

Adverse effects: rare but stinging may occur

Xylometazoline

ATC code: R01AA07

Nasal spray: 0.05%, LOU 4

Indications and dose

Adult

Different formulation is used

Paediatric

Relief of nasal congestion associated with acute and chronic rhinitis, common cold, sinusitis, to facilitate intranasal examination, by Nasal inhalation as nasal spray:

Child 6–12 years: 2 or 3 sprays into each nostril up to 3 times daily for a maximum of 5 days

Contraindications: Angle-closure glaucoma, avoid excessive or prolonged use, cardiovascular disease (in children), diabetes mellitus, elderly (in adults), hypertension, hyperthyroidism, ischaemic heart disease (in adults), prostatic hypertrophy (risk of acute retention) (in adults), rebound congestion.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Pregnancy: Manufacturer advises avoid.

Breastfeeding: Manufacturer advises caution—no information available.

Adverse effects: Systemic adverse effects are rare with intranasal use but children may be more susceptible to them, Transient burning, stinging, increased nasal discharge, rebound congestion with prolonged use (> 5 days). Hypertension, nausea, nervousness, dizziness, insomnia, headache.

Use of decongestants in infants and children under 6 years has been associated with agitated psychosis, ataxia, hallucinations, and even death—avoid

Interaction with other medicines (*indicates serious):

*MAOIs: concurrent use contraindicated, risk of hypertensive crisis.

*Phenelzine: concurrent use contraindicated, risk of hypertensive crisis.

*Tranylcypromine: concurrent use contraindicated, risk of hypertensive crisis.

Notes:

- Do not use this medicine more than recommended or for more than 5 days at a time as it can worsen the symptoms when treatment is stopped.
- Rebound congestion
- Sympathomimetic drugs are of limited value in the treatment of nasal congestion because they can, following prolonged use (more than 7 days), give rise to a rebound congestion (rhinitis medicamentosa) on withdrawal, due to a secondary vasodilatation with a subsequent temporary increase in nasal congestion. This in turn tempts the further use of the decongestant, leading to a vicious cycle of events

27.3. Medicines For the Throat & Mouth

Chlorhexidine

ATC code: R02AA05

Solution (mouthwash) , 0.2% (as gluconate/ digluconate), LOU 2

Indications and dose

Adult

Oral hygiene and plaque inhibition, oral candidiasis, gingivitis, managing aphthous ulcers, Oral using mouthwash: Rinse or gargle 10 mL twice daily (rinse or gargle for about 1 minute)

Managing dentures:

Cleanse and soak dentures in mouthwash solution for 15 minutes twice daily

Paediatric

Oral hygiene and plaque inhibition, oral candidiasis, gingivitis, managing aphthous ulcers, Oral using mouthwash:

Child (able to gargle): Rinse or gargle 10 mL twice daily (rinse or gargle for about 1 minute)

Adverse Effects: With oromucosal use Dry mouth, hypersensitivity, oral disorders, taste altered, tongue discolouration, tooth discolouration If desquamation occurs with mucosal irritation, discontinue treatment.

Notes:

» Patient and Caregiver advice: With oral (topical) use Chlorhexidine gluconate may be incompatible with some ingredients in toothpaste, rinse the mouth thoroughly with water between using toothpaste and chlorhexidine-containing product

Lidocaine Hcl

ATC code: N01BB52

Spray 10-mg metered dose (actuation), LOU 4

Indications and dose

Adult

Bronchoscopy, laryngoscopy, oesophagoscopy and endotracheal intubation: Up to 20 doses

Dental practice: 1–5 doses

Maxillary sinus puncture: 3 doses

Paediatric

Follow adult dosing

Contraindications: adjacent skin infection, inflamed skin,

Precautions: Avoid anaesthesia of the pharynx before meals - risk of choking, can damage plastic cuffs o endotracheal tubes

Allergy and cross-sensitivity: Hypersensitivity and cross-sensitivity Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine, reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

Hepatic impairment: Manufacturer advises caution (risk of increased exposure).

Renal impairment Possible accumulation of lidocaine and active metabolite, caution in severe impairment

Pregnancy: Crosses the placenta but not known to be harmful in animal studies—use if benefit outweighs risk. When used as a local anaesthetic, large doses can cause foetal bradycardia, if given during delivery can also cause neonatal respiratory depression, hypotonia, or bradycardia after paracervical or epidural block.

Breastfeeding: Present in milk but amount too small to be harmful.

Interactions with other medicines: antiarrhythmics

28.Medicines For Rheumatology

28.1. Medicines Used to Treat Gout

Allopurinol

ATC code: M04AA01

Tablet, 100 mg, 300 mg, LOU 4

Indications and dose

Adult

Gout, oral:

Mild: 100 mg/day PO initially; increased weekly to 200-300 mg/day

Moderate to severe: 100 mg/day PO initially; increased weekly to 400-600 mg/day

Note: Initiate 2–3 weeks after acute attack has subsided and administer a suitable NSAIM (not ibuprofen or a salicylate) or colchicine from the start of allopurinol treatment and continue for at least 1 month after correction of hyperuricaemia.

Paediatric: Used for other indications

Contraindications: previous allopurinol-induced rash. (if an acute attack occurs while receiving allopurinol, continue prophylaxis and treat attack separately).

Precautions: Ensure adequate fluid intake 2–3 L daily, renal impairment, hepatic impairment, pregnancy and breastfeeding, renal impairment, hepatic impairment, withdraw treatment if rash occurs (see below). For hyperuricaemia associated with cancer therapy, allopurinol should be started before cancer therapy.

Rash Risk of skin rash may be increased in patients receiving amoxicillin or ampicillin. The risk of hypersensitivity may also be increased in patients receiving thiazides or ACEIs. If a rash occurs, treatment should be stopped, treatment may be reintroduced if the rash is mild but discontinue immediately if it recurs

Hepatic impairment:

Reduce dose and monitor liver function.

Renal impairment:

Mild: no dosage reduction necessary.

Moderate: 50% of usual dose.

Severe: 30% of usual dose.

Adverse effects: rash (see Precautions above), hypersensitivity reactions occur rarely and include fever, lymphadenopathy, arthralgia, eosinophilia, erythema multiforme (SJS) or toxic epidermal necrolysis, vasculitis, hepatitis, renal impairment and, very rarely, seizures, GI disorders, rarely malaise, headache, vertigo, drowsiness, visual and taste disturbances, hypertension, alopecia, hepatotoxicity, paraesthesia, neuropathy, gynaecomastia, and blood disorders (including leukopenia, thrombocytopenia, haemolytic anaemia, and aplastic anaemia).

Interaction with other medicines (*indicates serious):

Amoxicillin: increased risk of rash and hypersensitivity.

Ampicillin: increased risk of rash and hypersensitivity.

Azathioprine: effects of azathioprine enhanced and toxicity increased, reduce dose of azathioprine.

Ciclosporin: plasma ciclosporin concentration possibly increased (risk of nephrotoxicity).

Cyclophosphamide: increased risk of cyclophosphamide toxicity.

Didanosine: increased plasma concentration of didanosine leading to didanosine toxicity.

Enalapril: increased risk of hypersensitivity.

Hydrochlorothiazide: increased risk of hypersensitivity, especially in renal impairment.

Mercaptopurine: effects of mercaptopurine enhanced and toxicity increased, reduce dose of mercaptopurine.

Theophylline: increased risk of theophylline toxicity.

Warfarin: anticoagulant effect possibly enhanced.

Colchicine

ATC code: MO4AC01

Tablet, 500 micrograms, LOU 4

Indications and dose

Adult

Acute gout, oral: 500 micrograms 2–4 times a day until symptoms relieved, maximum 6 mg per course, do not repeat course within 3 days

Short-term prophylaxis during initial therapy with allopurinol and uricosuric drugs, Oral: 500 micrograms twice daily

Paediatric

Child <16 years: Not recommended

Child >16 years

Treatment of acute gout flares, oral: 1mg at first sign of flare, then 0.5 mg 1 hr later; not to exceed 1.5 mg in 1-hr period

Prophylaxis, oral: 0.5 mg once daily or every 12hours; not to exceed 1mg/day; after gout flare, wait 12 hr to continue prophylaxis

Contraindications: Blood disorders

Precautions: Cardiac disease, elderly, GI disease

Interactions with other medicines: Moderate inhibitors of CYP3A4 – dose reduction by 50% required.

Potent inhibitors of CYP3A4 or P-glycoprotein inhibitors - dose reduction by 75% (to one quarter of usual dose) and avoid concurrent use in patients with hepatic or renal impairment.

Febuxostat

ATC code: MA4AA03

Tablet, 40 mg, LOU 5

Indications and dose

Adult

Treatment of chronic hyperuricaemia in gout, Oral:
Initially 80 mg once daily, if after 2–4 weeks of initial dose, serum uric acid is greater than 6 mg/100 mL then increase dose, increased if necessary to 120 mg once daily

Paediatric: Safety and efficacy not established

Contraindications: Not a treatment for acute gout but continue if attack develops when already receiving febuxostat, and treat attack separately

Precautions: Congestive heart failure, ischaemic heart disease, major cardiovascular disease, thyroid disorders, transplant recipients, Administer prophylactic NSAIM (not aspirin or salicylates) or colchicine for at least 6 months after starting febuxostat to avoid precipitating an acute attack.

Hepatic impairment: caution. Dose adjustments max. 80 mg daily in mild impairment, no dose information available in moderate to severe impairment.

Renal impairment: Use with caution if eGFR less than 30 mL/min/1.73 m2—no information available.

Pregnancy: avoid—limited information available.

Breastfeeding: avoid—present in milk in animal studies.

Adverse effects: Diarrhoea, gout aggravated, headache, hepatic disorders, nausea, oedema, skin reactions, Altered smell sensation, appetite abnormal, arrhythmias, arthritis, bundle branch block, chest discomfort, cholelithiasis, constipation, cough, diabetes mellitus, dizziness, drowsiness, dry mouth, dyspnoea, fatigue, GI discomfort, GI disorders, haemorrhage, hemiparesis, hyperlipidaemia, hypertension, increased risk of infection, insomnia, joint disorders, muscle complaints, muscle weakness, musculoskeletal pain, nephrolithiasis, palpitations, proteinuria, renal failure, sensation abnormal, sexual dysfunction, taste altered, urinary disorders, vasodilation, vomiting, weight changes, Agranulocytosis, alopecia, angioedema, hyperhidrosis, hypersensitivity, musculoskeletal stiffness, nephritis tubulointerstitial, nervousness, oral ulceration, pancreatitis, pancytopenia, rhabdomyolysis, SCARs, sudden cardiac death, thirst, thrombocytopenia, tinnitus, vision blurred

Interactions with other medicines: Aminophylline, Azathioprine, Carbamazepine, Efavirenz, Epirubicin, Interferon beta 1a,b, leflunomide, Mercaptopurine, Methotrexate, Phenobarbitone, Phenytoin, Remdesivir, Rfampicin, Theophylline

Notes:

- Pre-treatment screening: Monitor liver function tests before treatment as indicated.
- Monitoring requirements: Monitor liver function tests periodically during treatment as indicated.
- There have been rare but serious reports of hypersensitivity reactions, including SJS and acute anaphylactic shock with febuxostat. Patients should be advised of the signs and symptoms of severe hypersensitivity, febuxostat must be stopped immediately if these occur (early withdrawal is associated with a better prognosis), and must not be restarted in patients who have ever developed a hypersensitivity reaction to febuxostat. Most cases occur during the first month of treatment, a prior history of hypersensitivity to allopurinol and/or renal disease may indicate potential hypersensitivity to febuxostat
- Health care professionals are advised to avoid treatment with febuxostat in patients with pre-existing major cardiovascular disease (e.g., MI, stroke, or unstable angina), unless no other therapy options are appropriate, clinical guidelines for gout recommend treatment with febuxostat only when allopurinol is not tolerated or is contraindicated.

Probenecid

ATC code: M04AB01

Tablet, 250 mg, LOU 5

Indications and dose

Adult

To treat hyperuracaemia associated with chronic gout and hyperuracaemia caused by diuretic therapy, oral:
Initial dose 250 mg twice daily for a week to 500 mg twice daily and later increase dose to 500 mg every 4 weeks up to 2 g daily

Paediatric

To treat hyperuracaemia associated with chronic gout and hyperuracaemia caused by diuretic therapy, oral:

> 2 years and < 50 kg: dose of 25 kg/kg initially followed by 40 mg/kg given in 4 divided doses.

> 50 kg: usual adult dose recommended

Precautions: Peptic ulcers, Do not start during an acute attack of gout, Control of hyperuracaemia secondary to causes of cancer or cancer chemotherapy. History of renal calculi or blood disorders

Renal impairment: Not effective in chronic renal impairment particularly when GFR is less than 30 mL/min. Incase this happens increase fluid intake to reduce the risk of uric acid calculi

Adverse effects: Nausea, Vomiting, Anorexia, Headache, Sore gums, Flushing, Alopecia, Dizziness, Anaemia, Urinary frequency, Hypersensitivity reactions with fever, dermatitis, Pruritis, Urticaria, Rarely anaphylaxis and stevens Johnson syndrome have occurred

Interactions with other medicines: Diuretics or Pyrazinamide, Salicylates, Methotrexate, Ketorolac, Penicillins and Cephalosporins

28.2. Disease-Modifying Agents Used In Rheumatic Disorders (DMARDs) & Immunosuppressants Used In Rheumatology

Need to screen for TB, HIV and hepatitis viruses. Where possible, vaccinate prior to use. Biologic DMARDs require cold chain storage and transport.

Abatacept

ATC code: L04AA24

Powder for injection (IV), 250 mg, LOU 6

Indications and dose

Adult

Moderate-to-severe active rheumatoid arthritis (specialist use only), By IV infusion:

body weight up to 60 kg: 500 mg every 2 week for 3 doses, then 500 mg every 4 weeks, review treatment if no response within 6 months.

body weight 60–100 kg: 750 mg every 2 weeks for 3 doses, then 750 mg every 4 weeks, review treatment if no response within 6 months.

body weight 101 kg and above: 1 g every 2 weeks for 3 doses, then 1 g every 4 weeks, review treatment if no response within 6 months

Paediatric: Safety and efficacy not established

Contraindications: Severe infection

Precautions: Do not initiate until active infections are controlled, elderly (increased risk of adverse effects) predisposition to infection (screen for latent TB and viral hepatitis), progressive multifocal leucoencephalopathy (discontinue treatment if neurological symptoms present)

Conception and contraception: Effective contraception required during treatment and for 14 weeks after last dose.

Pregnancy: avoid unless essential.

Breastfeeding: Present in milk in animal studies—avoid breastfeeding during treatment and for 14 weeks after last dose.

Adverse effects: Asthenia, cough, diarrhoea, dizziness, GI discomfort, headaches hypertension, increased risk of infection, nausea, oral ulceration, skin reactions, vomiting, Alopecia, anxiety, arrhythmias, arthralgia. bruising tendency, conjunctivitis, depression, dry eye. dyspnoea, gastritis, hyperhidrosis, hypotension, influenza like illness, leucopenia, menstrual cycle, irregularities, neoplasms, pain in extremity, palpitations, paraesthesia, respiratory disorders, sepsis, sleep disorders throat tightness, thrombocytopenia, vasculitis, vasodilation, vertigo, visual acuity decreased, weight increased, Pelvic inflammatory disease

Interactions with other medicines: Anakinra, Rituximab, TNF blocking agent (such as Adalimumab, Etanercept, Infliximab)

Note:

» Directions for administration: For IV infusion, given intermittently in sodium chloride 0.9%, reconstitute each vial with 10 mL water for injections using the silicone-free syringe provided, dilute requisite dose in sodium chloride 0.9% to 100 mL (using the same silicone free syringe), give over 30 minutes through a low protein binding filter (pore size 0.2–1.2 micron).

Adalimumab

ATC code: L04AB04

Injection, 40 mg/0.4 mL, LOU 6

Indications and dose

Adult

Rheumatoid Arthritis, Active Psoriatic arthritis, Ankylosing Spondylitis, SC: 40mg every 2 weeks

Dosing considerations:

May be administered as monotherapy or combined with methotrexate or other non-biologic DMARDs

If not taken with concomitant methotrexate, additional benefit may be derived from increasing frequency to 40mg every week or increasing dose to 80mg every other week.

Moderate to severe chronic Plaque Psoriasis, Uveitis, SC: 80 mg once, then, after 1 week, 40mg every two weeks

Paediatric

See 28.3, Medicines for Juvenile Joint Diseases

Contraindications: Moderate or severe heart failure, severe infection

Precautions: Children should be brought up to date with current immunization schedule before initiating therapy, demyelinating disorders (risk of exacerbation), development of malignancy, do not initiate until active infections are controlled (discontinue if new serious infection develops), HBV—monitor for active infection, history of malignancy, mild heart failure (discontinue if symptoms develop or worsen), predisposition to infection

Active TB should be treated with standard treatment for at least 2 months before starting adalimumab. Patients who have previously received adequate treatment for TB can start adalimumab but should be monitored every 3 months for possible recurrence. In patients without active TB but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting adalimumab. In patients at high risk of TB who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with adalimumab.

Conception and contraception: Manufacturer advises effective contraception required during treatment and for at least 5 months after last dose.

Pregnancy: Avoid.

Breastfeeding: Avoid, manufacturer advises avoid for at least 5 months after last dose.

Adverse effects: Agranulocytosis, alopecia, anaemia,

anxiety, arrhythmias, arterial occlusion. asthma, broken nails, chest pain, coagulation disorder. connective tissue disorders, cough, dehydration. depression, dyspnoea, electrolyte imbalance, embolism and thrombosis, eye inflammation, fever, flushing, GI discomfort, GI disorders, haemorrhage, headaches, healing impaired, hyperglycaemia, hypersensitivity, hypertension, increased risk of infection, insomnia, leucocytosis, leucopenia, mood altered, muscle spasms, musculoskeletal pain, nausea, neoplasms, nerve disorders. neutropenia, oedema, renal impairment, seasonal allergy, sensation abnormal, sepsis, skin reactions, sweat changes, thrombocytopenia, vasculitis, vertigo, vision disorders, vomiting, Aortic aneurysm, congestive heart failure. demyelinating disorders, dysphagia, erectile dysfunction. gallbladder disorders, hearing impairment, hepatic disorders, inflammation, lupus erythematosus. meningitis viral, MI, nocturia. pancreatitis, respiratory disorders, rhabdomyolysis, sarcoidosis, solid organ neoplasm, stroke, tremor, Cardiac arrest, pancytopenia, SJS.

Associated with infections, sometimes severe, including TB, septicaemia, and hepatitis B reactivation.

Interactions with other medicines: Etanercept, Infliximab, Abatacept, Anakinra

Notes:

- Need to screen for TB, HIV and hepatitis viruses. Where possible, vaccinate prior to use
- Pre-treatment screening: TB Patients should be evaluated for TB before treatment.
- Monitoring requirements: Manufacturer advises monitor for infection before, during, and for 4 months after treatment. Manufacturer advises monitor for non-melanoma skin cancer before and during treatment, especially in patients with a history of PUVA treatment for psoriasis or extensive immunosuppressant therapy. For uveitis, manufacturer advises patients should be assessed for pre-existing or developing central demyelinating disorders before and at regular intervals during treatment.
- Patient and caregiver advice: An alert card should be provided.
- When used to treat hidradenitis suppurativa, patients and their caregivers should be advised to use a daily topical antiseptic wash on lesions during treatment with adalimumab.
- TB patients and their caregivers should be advised to seek medical attention if symptoms suggestive of TB (e.g., persistent cough, weight loss, or, and fever) develop.
- Blood disorders Patients and their caregivers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

Azathioprine

ATC CODE L04AX01

Tablet, 50 mg, LOU 4

Indications and dose

Adult

Rheumatoid arthritis, Oral: initially 1.5–2.5 mg/kg daily in divided doses, adjusted according to response, maintenance dose, 1–3 mg/kg daily, consider withdrawal if no improvement within 3 months.

Contraindications: hypersensitivity to azathioprine or mercaptopurine

Precautions: monitor for toxicity throughout treatment, monitor full blood counts frequently, hepatic impairment, renal impairment, elderly (reduce dose), pregnancy and breastfeeding, interactions.

Hepatic Impairment: Use with caution

Renal impairment: Use with caution

Pregnancy: Use with caution

Breastfeeding: Use with caution

Bone marrow suppression: Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example, unexplained bruising or bleeding, purpura, infection, or sore throat.

Adverse effects: hypersensitivity reactions requiring immediate and permanent withdrawal include malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension, and interstitial nephritis, dose-related bone marrow suppression, liver impairment, cholestatic jaundice, hair loss and increased susceptibility to infections and colitis in patients also receiving corticosteroids, nausea, rarely pancreatitis and pneumonitis, hepatic veno-occlusive disease, also herpes zoster infection.

Interaction with other medicines (*indicates serious):

*Allopurinol: effects of azathioprine enhanced and toxicity increased, reduce dose of azathioprine.

*Phenytoin: possibly reduced absorption of phenytoin.

*Sulfamethoxazole + trimethoprim: increased risk of haematological toxicity.

*Trimethoprim: increased risk of haematological toxicity.

*Live vaccines: avoid use of live vaccines with azathioprine (impairment of immune response).

*Warfarin: anticoagulant effect possibly reduced

Baricitinib

ATC code:L04AA37

Tablet, 2 mg, LOU 6

Indications and dose

Adult

For moderately to severely active rheumatoid arthritis when patients have had inadequate response to one or more tumor necrosis factor antagonist treatment: 2 mg PO every day

Contraindications:

Hypersensitivity to the active substance or to any of the excipients.

Pregnancy:

Precautions:

Baricitinib should only be used if no suitable treatment alternatives are available in patients:

65 years of age and older;

patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);

patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Baricitinib may increase risk for developing serious infections which may lead to hospitalization or death.

Avoid concomitant immunosuppressants (e.g, methotrexate, corticosteroids)

If a serious infection develops, interrupt dosing until infection is controlled.

Breastfeeding: Should not be used.

Adverse effects: Upper respiratory tract infections, Increased ALT/AST, nausea, platelet elevations, herpes zoster infection, herpes simplex infection, acne, neutropenia

Interactions with other medicines: *Immunosuppressive: possible risk of additive immunosuppression*

Cyclosporin (ciclosporin)

ATC code: L04AA01

Capsule, 25 mg, 100mg, LOU 6

Indications and dose

Adult

Indicated for severe active, rheumatoid arthritis where the disease has not adequately responded to methotrexate; may be used in combination with methotrexate.

Oral: 1.25 mg/kg twice daily; may increase by 0.5-0.75 mg/kg/day after 8 weeks and again after 12 weeks if needed, not to exceed 4 mg/kg/day

Discontinue if no improvement is observed by 16 weeks.

Decrease dose by 25-50% at any time to control adverse effects (eg, hypertension, elevations in serum creatinine >30% pretreatment level)

Contraindications: Hypersensitivity to ciclosporin or any component of formulations (e.g., polyoxyl 35 castor oil in injection or polyoxyl 40 hydrogenated castor oil in capsules), breastfeeding.

Precautions: Monitor kidney function (dose-dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction, exclude rejection if kidney transplant), monitor liver function (adjust dosage according to bilirubin and liver enzymes), monitor blood pressure (discontinue if hypertension cannot be controlled by antihypertensives), monitor serum potassium, particularly in marked renal impairment (risk of hyperkalaemia), monitor serum magnesium, hyperuricaemia, measure blood lipids before and during treatment, avoid in porphyria.

Additional cautions in nephrotic syndrome: Reduce dose by 25–50% if serum creatinine more than 30% above baseline at more than one measurement, perform renal biopsies at yearly intervals, contraindicated in uncontrolled infections and malignancy.

Renal impairment: Monitor kidney function, dose-dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction (exclude rejection if kidney transplant).

Hepatic impairment: May need dose adjustment based on bilirubin or liver enzyme levels.

Adverse effects: Common: Nephrotoxicity (dose-related and reversible increases in serum creatinine and urea unrelated to tissue rejection), gingival hyperplasia, hirsutism, headache, tremor, burning sensation in hands and feet during initial therapy, electrolyte disturbances including hyperkalaemia, hypomagnesaemia, hepatic dysfunction, hyperuricemia, hypercholesterolaemia, hyperglycaemia, hypertension (especially in heart transplant patients), increased incidence of malignancies and lymphoproliferative disorders, increased susceptibility to infections due to immunosuppression, increased insulin requirements, diabetes. GI disturbances, fatigue, myopathy or muscle weakness, gout. Rare: Confusion, coma, psychosis, allergic reactions, thrombocytopenia (sometimes with haemolytic uraemic syndrome), also mild anaemia, seizures, neuropathy, dysmenorrhoea or amenorrhoea, pancreatitis.

Interactions with other medicines (*indicates serious):

Aciclovir, Allopurinol, *Amikacin, *Amiloride, * Amphotericin B, *Azithromycin, * Carbamazepine, *Chloroquine, * Ciprofloxacin, *Contraceptives, *Digoxin, *Doxorubicin, * Doxycycline, *Enalapril, *Erythromycin, Etoposide, *Fluconazole, *Gentamicin, *Grapefruit juice, Griseofulvin, Hydrochlorothiazide, *ibuprofen, * Levofloxacin, *Levonorgestrel, *Medroxyprogesterone, * Methotrexate, *Metoclopramide, *Nelfinavir, *Norethisterone, *Ofloxacin, *Phenobarbital, *Phenytoin, *Potassium salts, Prednisolone, *Rifampicin, *Ritonavir, *Saquinavir, *Silver sulfadiazine, *Simvastatin, Spironolactone, Streptomycin, *Sulfadiazine, *Sulfadoxine+pyrimethamine, *Sulfamethoxazole+trimethoprim, *Trimethoprim, *avoid use of live vaccines, *Vancomycin, *Verapamil.

Notes:

- Lower doses are required when ciclosporin is used with other immunosuppressants. Concentrate for infusion may contain polyethoxylated castor oil, which has been associated with anaphylaxis, observe patient for 30 minutes after starting infusion and then at frequent intervals.
- Conversion: Any conversion between brands should be undertaken very carefully, and the manufacturer's product information consulted for further advice.
- Serum concentration monitoring: draw blood for ciclosporin measurement by venipuncture, not from a central line. Avoid using nonspecific assays which measure ciclosporin plus metabolites. Concentrations obtained from nonspecific assays are not interchangeable with the results from a specific assay.
- Consult local protocols or specialist advice for use in children.

- IV administration advice Dilute injection to 1:20 to 1:100 in glucose 5% or sodium chloride 0.9%, infuse IV over 2–6 hours (more slowly if facial flushing occurs), use a glass bottle and non-PVC administration set to avoid phthalate stripping and use short giving sets to reduce amount adsorbed.
- Patient information: Swallow capsules whole and take them 12 hours apart at the same times each day, clean your teeth and gums regularly.
- Hazardous agent. Use appropriate precautions for handling and disposal.

Etanercept

ATC code: L04AB01

Injection 25 mg, 50-mg vial, LOU 6

Indications and dose

Adult

Moderate-to-severe active rheumatoid arthritis (in combination with methotrexate or other synthetic DMARDs) when the response to other disease-modifying antirheumatic drugs is inadequate. Severe, active and progressive rheumatoid arthritis not previously treated with methotrexate. Active and progressive psoriatic arthritis when the response to other disease modifying antirheumatic drugs is inadequate, Severe active ankylosing spondylitis when the response to conventional therapy is inadequate. Severe, non-radiographic axial spondyloarthritis when the response to non-steroidal anti-inflammatory drugs is inadequate, by SC injection: 25 mg twice weekly, alternatively 50 mg once weekly, review treatment if no response within 12 weeks of initial dose

Moderate-to-severe plaque psoriasis when the response to other systemic therapies or psoralen and ultraviolet-A light (PUVA) is inadequate, or when these therapies cannot be used because of intolerance or contraindications, by SC injection: 25 mg twice weekly, alternatively 50 mg once weekly, alternatively 50 mg twice weekly for up to 12 weeks, followed by 25 mg twice weekly, alternatively 50 mg once weekly if required continue treatment for up to 24 weeks—continuous therapy beyond 24 weeks may be appropriate in some patients (consult product literature), discontinue if no response after 12 weeks

Contraindications: Active infection

Precautions: Development of malignancy, diabetes mellitus. heart failure (risk of exacerbation), HBV—monitor for active infection, hepatitis C infection (monitor for worsening infection), history of blood disorders, history of malignancy, history or increased risk of demyelinating disorders, pre disposition to infection (avoid i exposure to herpes zoster virus—interrupt treatment and consider varicella–zoster immunoglobulin. TB Active TB should be treated with standard treatment for at least 2 months before starting etanercept. Patients who have previously received adequate treatment for TB can start etanercept but should be monitored every 3 months for possible recurrence. In patients without active TB but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting etanercept. In patients at high risk of TB who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with etanercept.

Hepatic impairment Manufacturer advises caution in moderate to severe alcoholic hepatitis.

Conception and contraception: Manufacturer advises effective contraception required during treatment and for 3 weeks after last dose.

Pregnancy: Avoid—limited information available.

Breastfeeding: Manufacturer advises avoid—present in milk in animal studies.

Adverse effects: Cystitis, fever, hypersensitivity, increased risk of infection, pain, skin reactions, swelling Abscess, bursitis, cholecystitis, diarrhoea, endocarditis, eye inflammation, gastritis, hepatic disorders myositis, neoplasms, respiratory disorders, sepsis, skin ulcers, thrombocytopenia, vasculitis. Anaemia bone marrow disorders, congestive heart failure, cutaneous lupus erythematosus, demyelination, leucopenia, lupus-like syndrome, nerve disorders, neutropenia, sarcoidosis, seizure, SCARs, transverse myelitis. Dermatomyositis exacerbated, hepatitis B reactivation. Associated with infections, sometimes severe, including TB, septicaemia, and hepatitis B reactivation.

Interactions with other medicines: Some products that may interact with this drug include: abatacept, interleukin-1 blockers (such as anakinra, canakinumab, rilonacept), live vaccines (such as measles, mumps, polio, rubella, typhoid, varicella, yellow fever), other medications for autoimmune disease (such as azathioprine, cyclophosphamide).

Notes:

- **Pre-treatment screening:** TB Patients should be evaluated for TB before treatment.
- **Monitoring requirements**: Monitor for skin cancer before and during treatment, particularly in those at risk (including patients with psoriasis or a history of PUVA treatment).
- **Prescribing and dispensing information:** Etanercept is a biological medicine. Biological medicines must be prescribed and dispensed by brand name
- **Patient and caregiver advice:** Blood disorders- Patients and their caregivers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop. TB- Patients and their caregiver should be advised to seek medical attention if symptoms suggestive of TB (e.g., persistent cough, weight loss, and fever) develop. An alert card should be provided

Golimumab

ATC code: L04AB06

Injection solution (SC), 50 mg, LOU 6

Indications and dose

Adult

Ulcerative colitis (initiated by a specialist), by SC injection:

body weight up to 80 kg: Initially 200 mg, then 100

mg after 2 weeks, maintenance 50 mg every 4 weeks, alternatively maintenance 100 mg every 4 weeks, if inadequate response, review treatment if no response after 4 doses.

body weight 80 kg and above: Initially 200 mg, then 100 mg after 2 weeks, maintenance 100 mg every 4 weeks, review treatment if no response after 4 doses

Rheumatoid arthritis (initiated by a specialist). Psoriatic arthritis (initiated by a specialist). Ankylosing spondylitis (initiated by a specialist). Non-radiographic axial spondyloarthritis (initiated by a specialist), by SC injection:

body weight up to 100 kg: 50 mg once a month, on the same date each month, review treatment if no response after 3–4 doses.

body weight 100 kg and above: Initially 50 mg once a month for 3–4 doses, on the same date each month, dose may be increased if inadequate response, increased to 100 mg once a month, review treatment if inadequate response to this higher dose after 3–4 doses

Contraindications: Moderate or severe heart failure. severe active infection

Precautions: Active infection (do not initiate until active infections are controlled, discontinue if new serious infection develops until infection controlled), demyelinating disorders (risk of exacerbation), HBV—monitor for active infection, history or development of malignancy, mild heart failure (discontinue if symptoms develop or worsen), predisposition to infection, risk factors for dysplasia or carcinoma of the colon—screen for dysplasia regularly. TB Active TB should be treated with standard treatment for at least 2 months before starting golimumab. Patients who have previously received adequate treatment for TB can start golimumab but should be monitored every 3 months for possible recurrence. In patients without active TB but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting golimumab. In patients at high risk of TB who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with golimumab. Patients who have tested negative for latent TB, and those who are receiving or who have completed treatment for latent TB, should be monitored closely for symptoms of active infection.

Hepatic impairment, Manufacturer advises caution (no information available).

Conception and contraception: Manufacturer advises adequate contraception during treatment and for at least 6 months after last dose.

Pregnancy: Use only if essential.

Breastfeeding: Manufacturer advises avoid during and for at least 6 months after treatment—present in milk in animal studies.

Adverse effects: Abscess, alopecia, anaemia. asthenia, asthma, bone fracture, chest discomfort depression, dizziness, fever, GI discomfort, GI disorders, GI inflammatory disorders, headache, hypersensitivity, hypertension, increased risk of infection, insomnia, nausea, paraesthesia, respiratory disorders, skin reactions, stomatitis**.** Arrhythmia, balance impaired, bone marrow disorders, breast disorder, cholelithiasis, constipation, eye inflammation, eye irritation, flushing, goitre, hyperthyroidism, hypothyroidism, leucopenia, liver disorder, menstrual disorder, myocardial ischaemia, neoplasms, sepsis, thrombocytopenia, thrombosis, thyroid disorder, vision disorders Bladder disorder, congestive heart failure, demyelination, healing impaired, hepatitis B reactivation, lupus-like syndrome, Raynaud's phenomenon, renal disorder, sarcoidosis, taste altered, vasculitis. Associated with infections, sometimes severe, including TB septicaemia, and hepatitis B reactivation.

Interactions with other medicines: Some products that may interact with this drug include: other TNF-blockers (such as adalimumab, certolizumab, etanercept, infliximab), other drugs that weaken the immune system (such as abatacept, anakinra, cyclosporine).

Notes:

» Use in management of rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, juvenile idiopathic arthritis

Pre-treatment screening: TB Patients should be evaluated for TB before treatment.

Monitoring requirements: Monitor for infection before, during, and for 5 months after treatment.

Directions for administration, For doses requiring multiple injections, each injection should be administered at a different site. Missed dose If dose administered more than 2 weeks late, subsequent doses should be administered on the new monthly due date.

Patient and caregiver advice: TB All patients and their caregivers should be advised to seek medical attention if symptoms suggestive of TB (e.g., persistent cough, weight loss, and fever) develop. Blood disorders Patients and their caregivers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop. An alert card should be provided

Hydroxychloroquine

ATC code: P01BA02

Tablet 200 mg (as sulphate), LOU 4

Indications and dose

Adult

Active rheumatoid arthritis (administered on expert advice), Systemic and discoid lupus erythematosus (administered on expert advice, Oral: 200–400 mg daily, daily maximum dose to be based on ideal body weight, maximum 6.5 mg/kg per day

Precautions: Acute porphyrias, diabetes (may lower blood glucose), G6PD deficiency, maculopathy, may aggravate myasthenia gravis, may exacerbate psoriasis, neurological disorders (especially in those with a history of epilepsy may lower seizure threshold)

Hepatic impairment caution. consider dose adjustment in severe impairment.

Renal impairment: caution. Monitoring Monitor plasma-hydroxychloroquine concentration in severe renal impairment

Pregnancy: It is not necessary to withdraw an antimalarial drug during pregnancy if the rheumatic disease is well controlled, however, avoid use.

Breastfeeding: use with caution—present in milk in small amounts. Specialist sources. indicate risk of accumulation in infant due to long half life, monitor infant for symptoms of uveitis, e.g., eye redness or sensitivity to light.

Adverse effects: Abdominal pain, appetite decreased, diarrhoea, emotional lability, headache, nausea, skin reactions, vision disorders, vomiting, Alopecia, corneal oedema, dizziness, eye disorders, hair colour changes, nervousness, neuromuscular dysfunction, retinopathy, seizure. tinnitus, vertigo, Acute hepatic failure, agranulocytosis, anaemia, angioedema, bone marrow disorders, bronchospasm, cardiac conduction disorders, cardiomyopathy, hearing loss, hypoglycaemia leucopenia, movement disorders, muscle weakness, myopathy, photosensitivity reaction, psychosis, reflexes absent, SCARs, thrombocytopenia, tremor, ventricular hypertrophy, Overdose Hydroxychloroquine is very toxic in overdosage, overdosage is extremely hazardous and difficult to treat.

Interactions with other medicines: Taking digoxin with hydroxychloroquine may increase the levels of digoxin in the body, Insulin and other diabetes drugs, Drugs that affect heart rhythm, Certain malaria drugs, Antiseizure drugs, Immunosuppressant drugs**.**

Notes:

- Retinopathy: Recommendations on Monitoring. Recent data have highlighted that hydroxychloroquine retinopathy is more common than previously reported. Monitoring recommendations for hydroxychloroquine.
- Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).
- Do not use beyond 5 mg/kg body weight. Requires annual eye checkup

Infliximab

ATC code: LO4AB02

Powder for injection, 100 mg, LOU 6

Indications and dose

Adult

Severe active Crohn's disease, By IV infusion: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, then 5 mg/kg after 4 weeks, if condition has responded, then maintenance 5 mg/kg every 8 weeks

Fistulating Crohn's disease, By IV infusion: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, if condition has responded consult product literature for guidance on further doses

Severe active ulcerative colitis, By IV infusion: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every 8 weeks, discontinue if no response 14 weeks after initial dose

Rheumatoid arthritis (in combination with methotrexate), By IV infusion: Initially 3 mg/kg, then 3 mg/kg after 2 weeks, followed by 3 mg/kg after 4 weeks, then 3 mg/kg every 8 weeks, dose to be increased only if response is inadequate after 12 weeks of initial treatment, increased in steps of 1.5 mg/kg every 8 weeks, increased if necessary up to 7.5 mg/kg every 8 weeks, alternatively increased if necessary to 3 mg/kg every 4 weeks, discontinue if no response by 12 weeks of initial infusion or after dose adjustment

Ankylosing spondylitis, By IV infusion: 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every 6–8 weeks, discontinue if no response by 6 weeks of initial infusion

Psoriatic arthritis (in combination with methotrexate), By IV infusion: 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, followed by 5 mg/kg every 8 weeks

Plaque psoriasis, By IV infusion: 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every 8 weeks, discontinue if no response within 14 weeks of initial infusion

Contraindications: Moderate or severe heart failure, severe infections

Precautions: Demyelinating disorders (risk of exacerbation), dermatomyositis, development of malignancy, HBV—monitor for active infection, history of colon carcinoma (in inflammatory bowel disease), history of dysplasia (in inflammatory bowel disease), history of malignancy, history of prolonged immunosuppressant or PUVA treatment in patients with psoriasis, mild heart failure (discontinue if symptoms develop or worsen). predisposition to infection (discontinue if new serious infection develops), risk of delayed hypersensitivity reactions if drug-free interval exceeds 16 weeks (re-administration after interval exceeding 16 weeks not recommended)

Infection Manufacturer advises patients should be up-to-date with current immunisation schedule before initiating treatment.

TB Manufacturer advises to evaluate patients for active and latent TB before treatment. Active TB should be treated with standard treatment for at least 2 months before starting infliximab. If latent TB is diagnosed, treatment should be started before commencing treatment with infliximab. Patients who have previously received adequate treatment for TB can start infliximab but should be monitored every 3 months for possible recurrence. In patients without active TB but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting infliximab. In patients at high risk of TB who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with infliximab. Patients should be advised to seek medical attention if symptoms suggestive of TB develop (e.g., persistent cough, weight loss and fever).

Hypersensitivity reactions (including fever, chest pain, hypotension, hypertension, dyspnoea, transient visual loss, pruritus, urticaria, serum sickness-like reactions, angioedema, anaphylaxis) reported during or within 1–2 hours after infusion (risk greatest during first or second infusion or in patients who discontinue other immunosuppressants). Manufacturer advises prophylactic antipyretics, antihistamines, or hydrocortisone may be administered.

Conception and contraception: Manufacturer advises adequate contraception during and for at least 6 months after last dose.

Pregnancy: Use only if essential.

Breastfeeding: Amount probably too small to be harmful.

Adverse effects: Abscess, alopecia, anaemia. arrhythmias, arthralgia, chest pain, chills, constipation decreased leucocytes, depression, diarrhoea, dizziness, dyspnoea, eye inflammation, fatigue, fever GI discomfort, GI disorders, haemorrhage, headache, hepatic disorders, hyperhidrosis, hypertension, hypotension, increased risk of infection, infusion related reaction, insomnia, lymphadenopathy, myalgia, nausea, neutropenia, oedema, pain, palpitations, respiratory disorders, sensation abnormal, sepsis, skin reactions, vasodilation, vertigo. Anxiety, cheilitis, cholecystitis, confusion, drowsiness, healing impaired, heart failure, hypersensitivity, lupus-like syndrome, lymphocytosis, memory loss, neoplasms, nerve disorders, pancreatitis, peripheral ischaemia, pulmonary oedema, seborrhoea, seizure, syncope, thrombocytopenia, thrombophlebitis Agranulocytosis, circulatory collapse, cyanosis, demyelinating disorders, granuloma, haemolytic anaemia, hepatitis B reactivation, meningitis, pancytopenia, pericardial effusion, sarcoidosis, SCARs, transverse myelitis, vasculitis, vasospasm. Dermatomyositis exacerbated, hepatosplenic T-cell lymphoma (increased risk in inflammatory bowel disease), MI, myocardial ischaemia, vision loss.

Interactions with other medicines: Activated charcoal, Fish oils (omega-3 polyunsaturated fatty acids), Azathioprine, Atorvastatin, Esomeprazole, Acetaminophen, Quetipine, Rivaroxaban, Cetrizine.

Notes:

» Use in management of rheumatoid arthritis, Crohn's disease, vasculitis, psoriatic arthritis, axial spondyloarthritis

Important safety information: Adequate resuscitation facilities must be available when infliximab is used.

Pre-treatment screening, TB Manufacturer advises patients should be evaluated for TB before treatment.

Monitoring requirements, Monitor for infection before, during, and for 6 months

after treatment. All patients should be observed carefully for 1–2 hours after infusion and resuscitation equipment should be available for immediate use (risk of hypersensitivity reactions). Monitor for symptoms of delayed hypersensitivity if readministered after a prolonged period. Manufacturer advises periodic skin examination for nonmelanoma skin cancer, particularly in patients with risk factors.

Directions for administration, For IV infusion, give intermittently in sodium chloride 0.9%, reconstitute each 100-mg vial with 10 mL water for injections using a 21-gauge or smaller needle, gently swirl vial without shaking to dissolve, allow to stand for 5 minutes, dilute requisite dose with infusion fluid to a final volume of 250 mL and give through a low protein binding filter (1.2 micron or less) over at least 2 hours (adults over 18 years who have tolerated 3 initial 2-hour infusions may be given subsequent infusions of up to 6 mg/kg over at least 1 hour), start infusion within 3 hours of reconstitution.

Prescribing and dispensing information: Infliximab is a biological medicine. Biological medicines must be prescribed and dispensed by brand name,

Patient and caregiver advice-TB Patients and caregivers should be advised to seek medical attention if symptoms suggestive of TB (e.g., persistent cough, weight loss, and fever) develop.

Blood disorders Patients and caregivers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

Hypersensitivity reactions Patients and caregivers should be advised to keep Alert card with them at all times and seek medical advice if symptoms of delayed hypersensitivity develop.

Alert card should be provided

Leflunomide

ATC code: L04AA13

Tablets. 20 mg, LOU 6

Indications and dose

Adult

Rheumatoid arthritis, oral: Initially 100 mg once daily for 3 days, then reduced to 10–20 mg once daily

Active psoriatic arthritis, Oral: Initially 100 mg once daily for 3 days, then reduced to 20 mg once daily

Contraindications Serious infection. severe hypoproteinemia, severe immunodeficiency

Precautions Anaemia (avoid if significant and due to causes other than rheumatoid arthritis), history of TB, impaired bone-marrow function (avoid if significant and due to causes other than rheumatoid arthritis), leucopenia (avoid if significant and due to causes other than rheumatoid arthritis) thrombocytopenia (avoid if significant and due to causes other than rheumatoid arthritis)

Discontinue treatment and institute washout procedure in case of serious side-effect (consult product literature). Hepatotoxicity Potentially life-threatening hepatotoxicity reported usually in the first 6 months.

Discontinue treatment (and institute washout procedure—consult product literature) or reduce dose according to liver-function abnormality, if liver-function abnormality persists after dose reduction, discontinue treatment and institute washout procedure.

Hepatic impairment: avoid—active metabolite may accumulate.

Renal impairment: avoid in moderate or severe impairment

Conception and contraception Effective contraception essential during treatment and for at least 2 years after treatment in women and at least 3 months after treatment in men (plasma concentration monitoring required, waiting time before conception may be reduced with washout procedure—consult product literature). The concentration of the active metabolite

after washout should be less than 20 micrograms/L (measured on 2 occasions 14 days apart) in men or women before conception—consult product literature.

Pregnancy: Avoid—active metabolite teratogenic in animal studies.

Breastfeeding: Present in milk in animal studies- avoid.

Adverse effects: Abdominal pain, accelerated hair loss, appetite decreased, asthenia, diarrhoea, dizziness, GI disorders, headache, leucopenia, nausea, oral disorders, paraesthesia, peripheral neuropathy, skin reactions, tendon disorders, vomiting, weight decreased**,** Anaemia, anxiety, electrolyte imbalance, hyperlipidaemia, taste altered, thrombocytopenia**,** Agranulocytosis, eosinophilia, hepatic disorders, infection, pancreatitis, pancytopenia, respiratory disorders, sepsis, SCARs, vasculitis Cutaneous lupus erythematosus, hypouricaemia pulmonary hypertension, renal failure

Interaction with other medicines: Warfarin, Rifamycins, Methotrexate, Cholestyramine, Tacrolimus, Ciclosporin

Notes:

- Use with CAUTION in women of child-bearing potential. Use only when methotrexate and sulfasalazine cannot be used
- Pre-treatment screening: Exclude pregnancy before treatment.
- Monitoring requirements: Monitor full blood count (including differential white cell count and platelet count) before treatment and every 2 weeks for 6 months then every 8 weeks. Monitor liver function before treatment and every 2 weeks for first 6 months then every 8 weeks. Monitor blood pressure.
- Treatment cessation: Washout Procedure The active metabolite persists for a long period, to aid drug elimination in case of serious adverse effect, or before starting another disease-modifying antirheumatic drug, or before conception, stop treatment and give either colestyramine or charcoal, activated Procedure may be repeated as necessary

Methotrexate

ATC code: LO4AX03

Tablet, 2.5 mg (as sodium salt), LOU 4

Injection (prefilled syringe), 10 mg/mL (0.4 mL) and 25 mg/mL (0.4 mL), LOU 4

Indications and dose

Adult

Rheumatoid arthritis, psoriatic arthritis and other systemic rheumatic diseases

Administered on expert advice.

For Rheumatoid arthritis, ora/IV/IMI: 7.5 mg once **weekly** (as a single dose), adjusted according to response, maximum total dose, 25 mg **weekly.**

Methotrexate is considered the anchor drug (unless contraindicated) for rheumatoid arthritis

Contraindications: pregnancy and breastfeeding, immunodeficiency syndromes,.

Precautions: monitor throughout treatment (including blood counts and hepatic and renal function tests), renal impairment (avoid if moderate or severe, hepatic impairment (avoid if severe), reduce dose or withdraw if acute infection develops, advise men and women to use contraception during, and for at least 6 months after, treatment, peptic ulceration, ulcerative colitis, diarrhoea, ulcerative stomatitis, advise patient to avoid self-medication with salicylates or other NSAIMs, warn patient with rheumatoid arthritis to report cough or dyspnoea.

Adverse effects: blood disorders (bone marrow suppression), liver damage, pulmonary toxicity, GI disturbances - if stomatitis and diarrhoea occur, stop treatment, renal failure, skin reactions, alopecia, osteoporosis, arthralgia, myalgia, ocular irritation, precipitation of diabetes

Interactions with other medicines: Acetylsalicylic acid, Amoxicillin, Ampicillin, Benzylpenicillin, Ciclosporin, Cisplatin, Dexamethasone, Doxycycline, Hydrocortisone, Ibuprofen, Nitrous oxide, Phenoxymethylpenicillin Phenytoin, Prednisolone, Pyrimethamine, Silver sulfadiazine, Sulfadiazine, Sulfadoxine + pyrimethamine, Sulfamethoxazole + trimethoprim, Trimethoprim

Notes:

Use with **CAUTION** in women of child-bearing potential.

Bone marrow suppression. Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example, unexplained bruising or bleeding, purpura, infection, or sore throat.

Important. The doses are weekly doses and care is required to ensure that the correct dose is prescribed and dispensed.

Methylprednisolone

ATC code: H02AB04

Powder for injection 125 mg (as sodium succinate), LOU 4

Powder for injection 500 mg (as sodium succinate), LOU 4

Indications and dose

Adult

Suppression of inflammatory and allergic disorders, severe rheumatic disorders, e.g., Lupus Nephritis, Neuro Lupus, Systemic Vasculitis, By slow IV injection, or By IV infusion: Initially 10–500 mg.

Treatment of relapse in multiple sclerosis when oral steroids have failed or have not been tolerated, or in those who require hospital admission, By IV infusion: 1 g once daily for 3–5 days

Paediatric

Severe erythema multiforme, Lupus nephritis, Systemic onset juvenile idiopathic arthritis BY IV infusion:

Child: 10–30 mg/kg once daily or on alternate days (max. per dose 1 g) for up to 3 doses

Precautions: With IV use Rapid IV administration of large doses associated with cardiovascular collapse

With systemic use Systemic sclerosis (increased incidence of scleroderma renal crisis)

Adverse effects: Common or very common: With parenteral use Confusion, delusions, depressed mood, diarrhoea, dizziness, dyslipidaemia, hallucination, hiccups, Kaposi's sarcoma, lipomatosis, oedema, schizophrenia, suicidal thoughts, vomiting, withdrawal syndrome

Interactions with other medicines: *See Prednisolone*

Notes:

Methylprednisolone exerts predominantly glucocorticoid effects with minimal mineral corticoid effects

Prednisolone

ATC code: R01AD02

Tablet, 5 mg, 20 mg LOU 5

Tablet, 20 mg, LOU 5

Indications and dose

Adult

Systemic Autoimmune disorders: SLE, Myositis, Rheumatoid Arthritis (as add on therapy), Vasculitis, Sarcoidosis, Scleroderma, Oral: severe disease 1 mg/kg. Consider steroid taper as soon as clinical condition allows

Contraindications: untreated bacterial, viral, and fungal infections, avoid live virus vaccines.

Precautions: monitor body weight, blood pressure, fluid and electrolyte balance, and blood glucose concentration throughout treatment, adrenal suppression during and for some months after withdrawal (intercurrent infection or surgery may require increased dose of corticosteroid or temporary reintroduction if already withdrawn), quiescent amoebiasis, strongyloidiasis, or TB possibly reactivated, increased severity of

viral infections, particularly chickenpox and measles (passive immunization with immunoglobulin required), hypertension, recent, congestive heart failure, elderly, children and adolescents (growth retardation possibly reversible), renal impairment hepatic impairment diabetes mellitus, osteoporosis, glaucoma, corneal perforation, severe psychosis, epilepsy, psoriasis, peptic ulcer, hypothyroidism, history of steroid myopathy, pregnancy and breastfeeding interactions.

Adverse effects: GI effects including dyspepsia, oesophageal

ulceration, development of or aggravation of peptic ulcers, abdominal distension, acute pancreatitis, increased appetite and weight gain, adrenal suppression with high doses, leading to cushingoid symptoms (moon face, acne, bruising, abdominal striae, truncal obesity, muscle wasting), menstrual irregularities and amenorrhoea, hypertension, osteoporosis, with resultant vertebral collapse and long-bone fractures, avascular osteonecrosis, ophthalmic effects including glaucoma, subcapsular cataracts, exacerbation of viral or fungal eye infections, diabetes mellitus, thromboembolism,

Notes:

- Prednisolone is a representative corticosteroid with mainly glucocorticoid activity. Various drugs can serve as alternatives.
- Prednisolone is a complementary list medicine for the treatment of systemic rheumatic diseases.

Rituximab

ATC code: L01XC02

Injection (IV), 10 mg/mL 10 mL, 50 mL, LOU 6

Indications and dose

Adult

Rheumatoid arthritis (specialist use only), By IV infusion: 1 g, then 1 g after 2 weeks, consult product literature for information on retreatment

SLE (specialist use only), By IV infusion: 1 g, then 1 g after 2 weeks, consult product literature for information on retreatment

Vasculitis, Interstial Lung Disease (specialist use only), By IV infusion:1 g, then 1 g after 2 weeks, consult product literature for information on retreatment

*Pemphigus vulgaris (specialist use only), By IV infusion:*1 g, then 1 g after 2 weeks, maintenance 0.5 g, at months 12 and 18, and then every 6 months thereafter if needed, consult product literature for the treatment of relapse

Contraindications: Severe infection

Specific contraindications, When used for granulomatosis with polyangiitis and microscopic polyangiitis, pemphigus vulgaris, or rheumatoid arthritis Severe heart failure, severe, uncontrolled heart disease

For full details on contraindications, consult product literature.

General precautions: History of cardiovascular disease, exacerbation of angina, arrhythmia, and heart failure have been reported, patients receiving cardiotoxic chemotherapy, exacerbation of angina, arrhythmia, and heart failure have been reported, pre-medication recommended to minimise adverse reactions (consult product literature), predisposition to infection, transient hypotension occurs frequently during infusion (antihypertensives may need to be withheld for 12 hours before infusion)

Specific precautions: When used for granulomatosis with polyangiitis and microscopic polyangiitis, or pemphigus vulgaris Pneumocystis jirovecii pneumonia—consult product literature for prophylaxis requirements

For full details on cautions, consult product literature or local treatment protocol. Hepatitis B infection and reactivation hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking rituximab. Patients with positive hepatitis B serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation, treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately

treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for up to a year following the last infusion (consult product literature).

Conception and contraception: Effective contraception (in both sexes) required during and for 12 months after treatment.

Pregnancy: Avoid unless potential benefit to mother outweighs risk of B-lymphocyte depletion in fetus.

Breastfeeding, Avoid breastfeeding during and for 12 months after treatment.

Adverse effects, Angioedema, anxiety, appetite decreased, arrhythmias, bone marrow disorders, bursitis cancer pain, cardiac disorder, chest pain, chills, dizziness dysphagia, dyspnoea, ear pain, electrolyte imbalance, GI discomfort, GI disorders, hepatitis B, hypercholesterolaemia, hyperglycaemia, hyperhidrosis, hypertension, hypotension, insomnia, lacrimation disorder, malaise, migraine, multi organ failure, muscle complaints, muscle tone increased, nausea, nerve disorders, oedema, oral disorders, osteoarthritis, respiratory disorders, sensation abnormal, sepsis, skin reactions, throat irritation, tinnitus, vasodilation, weight decreased. Asthma, coagulation disorder, heart failure, hypoxia, ischaemic heart disease, lymphadenopathy, taste altered. Cytokine release syndrome, facial paralysis, renal failure, SJS (discontinue), toxic epidermal necrolysis (discontinue), tumour lysis syndrome, vasculitis, vision disorders. Epistaxis, hearing loss hypogammaglobulinaemia, infective thrombosis, influenza like illness, irritability, muscle weakness, nasal congestion, posterior reversible encephalopathy syndrome, psychiatric disorder, seizure, skin papilloma, tremor

Adverse effects, further information: Associated with infections, sometimes severe, including TB, septicaemia, and hepatitis B reactivation. Progressive multifocal leucoencephalopathy has been reported in association with rituximab, patients should be monitored for cognitive, neurological, or psychiatric signs and symptoms. If progressive multifocal leucoencephalopathy is suspected, suspend treatment until it has been excluded.

Interactions with other medicines: Zolpidem, Celecoxib, Mycophenolate mofetil, Duloxetine, Apixaban, Fish oil (omega-3 polyunsaturated fatty acids) Furosemide, Pregabalin, Esomeprazole, Acetaminophen, Hydroxychloroquine, Levothyroxine, Ascorbic acid, Ondasentron, Cholecalciferol

Notes:

- Use in management of rheumatoid arthritis, Lupus, vasculitis, myositis
- Monitoring requirements: For full details on monitoring requirements consult product literature.
- Directions for administration, With IV use For IV infusion, give intermittently in glucose 5% or sodium chloride 0.9%, dilute to 1–4 mg/mL and gently invert bag to avoid foaming, for further information, consult product literature.
- Prescribing and dispensing information, Rituximab is a biological medicine. Biological medicines must be prescribed and dispensed by brand name
- Patient and caregiver advice: Alert card
- When used for Granulomatosis with polyangiitis and microscopic polyangiitis or Rheumatoid arthritis or Pemphigus vulgaris Patients should be provided with a patient alert card with each infusion.

Sulfasalazine

ATC code: A07EC01

Tablet, 500 mg, LOU 4

Indications and dose

Adult

Rheumatoid arthritis, ulcerative colitis and Crohn disease (Administered on expert advice) oral (as gastro-resistant tablets): initially 500 mg daily, increased by 500 mg at intervals of 1 week to a maximum of 2–3 g daily in divided doses.

Contraindications: hypersensitivity to salicylates and sulfonamides, severe renal impairment, child under 2 years, porphyria.

Precautions: monitor blood counts and liver function during first 3 months of treatment, monitor renal function regularly, renal impairment, pregnancy and breastfeeding, history of allergy, G6PD deficiency, slow acetylator status,

Bone marrow suppression. Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example, unexplained bruising or bleeding, purpura, infection, or sore throat.

Adverse effects: nausea, diarrhoea, headache, loss of appetite, fever, blood disorders (including Heinz body anaemia, megaloblastic anaemia, leukopenia, neutropenia, and thrombocytopenia), hypersensitivity reactions (including rash, urticaria, erythema multiforme (SJS), exfoliative dermatitis, epidermal necrolysis, pruritus, photosensitization, anaphylaxis, serum sickness, interstitial nephritis, and lupus erythematosus- like syndrome), lung complications (including eosinophilia and fibrosing alveolitis), ocular complications (including periorbital oedema), stomatitis, parotitis, ataxia, aseptic meningitis, vertigo, tinnitus, alopecia, peripheral neuropathy, insomnia, depression, hallucinations, renal effects (including proteinuria, crystalluria, and haematuria), oligospermia, rarely acute pancreatitis, hepatitis, urine may be coloured orange, some soft contact lenses may be stained.

Interactions with other medicines: Azathioprine, Digoxin, Folic and Folinic acid, Mercaptopurine.

Tocilizumab

ATC code: L04AC07

Injection (solution for IV infusion) ,20 mg/mL (4-mL vial), LOU 6

Injection, single use prefilled syringe for subcutaneous injection, 162mg/0.9mL, LOU 6

Indications and dose

Adult

Rheumatoid arthritis [severe, active and progressive, not previously treated with methotrexate]. Rheumatoid arthritis [moderate-to-severe, in combination with methotrexate or alone if methotrexate inappropriate, when response to at least one disease-modifying antirheumatic drug or tumour necrosis factor inhibitor has been inadequate, or in those who are intolerant of these drugs],

By IV infusion: 8 mg/kg every 4 weeks (max. per dose 800 mg), for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count—consult product literature.

By SC Injection:

Weight <100 kg: 162 mg every other week, followed by an increase to weekly based on clinical response.

Weight ≥100 kg: 162 mg weekly

Contraindications: Do not initiate if absolute neutrophil count less than 26109/L, severe active infection

Precautions: History of diverticulitis, history of intestinal ulceration, history of recurrent or chronic infection (interrupt treatment if serious infection occurs), low absolute neutrophil count, low platelet count, predisposition to infection (interrupt treatment if serious infection occurs)

Precautions, further information: TB Patients with latent TB should be treated with standard therapy before starting tocilizumab.

Hepatic impairment Manufacturer advises caution—consult product literature.

Renal impairment, With IV use Manufacturer advises monitor renal function closely in moderate-to-severe impairment—no information available.

With SC use Manufacturer advises monitor renal function closely in severe impairment—no information available.

Conception and contraception: Effective contraception required during and for 3 months after treatment.

Pregnancy: Manufacturer advises avoid unless essential—toxicity in animal studies.

Breastfeeding Manufacturer advises avoid—no information available.

Adverse effects: Abdominal pain, conjunctivitis, cough, dizziness, dyslipidaemia, dyspnoea, GI disorders, headache, hypersensitivity, hypertension, increased risk of infection, leucopenia, neutropenia, oral disorders, peripheral oedema, skin reactions, weight increased Hypothyroidism, nephrolithiasis**,** Hepatic disorders, infusion related**,** reaction, interstitial lung disease, pancytopenia, Stevens- Johnson syndrome

Adverse effects, further information: Neutrophil and platelet counts Manufacturer advises discontinue if absolute neutrophil count less than 0.56109/L or platelet count less than 506103/microlitre. Abnormal hepatic function Manufacturer advises caution if hepatic enzymes more than 1.5 times the upper limit of normal. Manufacturer advises discontinue if hepatic enzymes more than 5 times the upper limit of normal.

Interactions with other medicines: Celecoxib, Duloxetine, Fish oil (omega-3 polyunsaturated fatty acids) Esomeprazole, Acetaminophen, Ascorbic acid, Cholecalciferol, Acetylsalicylic acid, Amoxicillin/clavulanic acid, Calcium/vitamin D, Fluconazole, Ethanol, Atorvastatin, Metoprolol, Budesonide/formoterol, Tramadol

Notes:

- IMPORTANT SAFETY INFORMATION ADVICE: TOCILIZUMAB RARE RISK OF SERIOUS LIVER INJURY INCLUDING CASES REQUIRING TRANSPLANTATION (JULY 2019). There have been reports of rare but serious cases of drug-induced liver injury, including acute liver failure and hepatitis, in patients treated with tocilizumab, some cases required liver transplantation. Serious liver injury was reported from 2 weeks to more than 5 years after initiation of tocilizumab.
- Health care professionals are advised to initiate tocilizumab treatment with caution in patients with hepatic transaminases (ALT or AST) more than 1.5 times the upper limit of normal (ULN), initiation is not recommended in those with ALT or AST more than 5 times the ULN (see Monitoring requirements). Patients and their caregivers should be advised to seek immediate medical attention if signs and symptoms of liver injury, such as tiredness, abdominal pain, and jaundice, occur. Use in management of rheumatoid arthritis, giant cell arthritis

Pre-treatment screening: TB Patients should be evaluated for TB before treatment.

Monitoring requirements: Manufacturer advises monitor lipid profile 4–8 weeks after starting treatment and then as indicated. Manufacturer advises monitor for demyelinating disorders. Manufacturer advises monitor hepatic transaminases before starting treatment, every 4–8 weeks for first 6 months of treatment, then every 12 weeks thereafter. Manufacturer advises monitor neutrophil and platelet count before starting treatment, 4–8 weeks after starting treatment and then as indicated.

Directions for administration: With IV use For IV infusion, manufacturer advises give intermittently in sodium chloride 0.9%, dilute requisite dose to a volume of 100 mL with infusion fluid and give over 1 hour.

With SC use preparation specific for SC injection, manufacturer advises rotate injection site and avoid skin that is tender, damaged or scarred. Patients may self administer Tocilizumab after appropriate training in SC injection technique.

Prescribing and dispensing information: Manufacturer advises to record the brand name and batch number after each administration.

Handling and storage, protect from light and store in a refrigerator (2–8 °C)—consult product literature for further information regarding storage conditions outside refrigerator and after preparation of the infusion.

Patient and caregiver advice: patients and their caregivers should be advised to seek immediate medical attention if symptoms of infection occur, or if symptoms of diverticular perforation such as abdominal pain, haemorrhage, or fever accompanying

change in bowel habits occur.

An alert card should be provided.

Driving and skilled tasks - patients should be counselled on the effects on driving and performance of skilled tasks—increased risk of dizziness.

Triamcinolone

ATC code: S01BA05

Injection (suspension), 40mg/1mL amp (as acetonide or hexacetonide), LOU5

Indications and dose

Adult

Rheumatic and Arthritic Disorders, IM: 60 mg every 6 weeks; may be supplemented by an additional 20 – 100 mg when required (PRN).

Rheumatic and Arthritic Disorders, Intra-articular/ Intrasynovial /soft-tissue injection: Large joints, 15 – 40 mg; small joints / tendon sheath inflammation, 2.5 – 10 mg

Contraindications, Precautions, Adverse effects, Interaction with other medicines, Notes: See Section 22.2

28.3. Medicines For Juvenile Joint Diseases

Acetylsalicylic acid (Aspirin)

ATC code: N02BA01

Tablet (scored), 300 mg, LOU 4

Indications and dose

Paediatric

Juvenile arthritis, rheumatic fever, oral:

Infant or **child:** Up to 130 mg/kg daily in 5–6 divided doses in acute conditions, 80–100 mg/kg daily in divided doses for maintenance

Kawasaki disease, oral:

Neonate: Initially 8 mg/kg four times daily until afebrile, followed by 5 mg/kg once daily for 6–8 weeks; if no evidence of coronary lesions after 8 weeks, discontinue treatment or seek expert advice.

Infant or **child:** Initially 7.5–12.5 mg/kg four times daily until afebrile, followed by 2–5 mg/kg once daily for 6–8 weeks; if no evidence of coronary lesions after 8 weeks, discontinue treatment or seek expert advice.

Contraindications: Hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAIM, for simple analgesia and antipyrexia in children under 16 years (risk of Reye syndrome), active peptic ulceration, haemophilia and other bleeding disorders, hepatic failure.

Precautions: Asthma, uncontrolled hypertension, concomitant use of drugs that increase risk of bleeding, previous peptic ulceration, G6PD deficiency, dehydration, renal impairment, hepatic impairment.

Hepatic impairment: Avoid in severe hepatic impairment, increased risk of GI bleeding.

Renal impairment: Increased risk of bleeding and acetylsalicylic acid induced renal impairment.

Severe: avoid, increased risk of sodium and water retention, deterioration in renal function, GI bleeding.

Adverse effects: Common: Nausea, dyspepsia, GI ulceration or bleeding, tinnitus, vertigo, confusion, increased bleeding time. Hypersensitivity reactions including angioedema, bronchospasm and rash (including SJS), iron deficiency anaemia, renal impairment, oesophageal ulceration. Major haemorrhage (including GI, subconjunctival or other), blood dyscrasias, oedema, myocarditis, Reye syndrome with subsequent encephalopathy and severe hepatic injury.

Interaction with other medicines (*indicates serious):

Dexamethasone: increased risk of GI bleeding and ulceration, dexamethasone reduces plasma salicylate concentration.

Fluoxetine: increased risk of bleeding.

*Heparin: enhanced anticoagulant effect of heparin.

Hydrocortisone: increased risk of GI bleeding and ulceration, hydrocortisone reduces plasma salicylate concentration.

*Ibuprofen: avoid concomitant use (increased adverse effects), antiplatelet effect of acetylsalicylic acid possibly reduced.

*Methotrexate: reduced excretion of methotrexate (increased toxicity).

Metoclopramide: enhanced effect of acetylsalicylic acid (increased rate of absorption).

Phenytoin: enhancement of effect of phenytoin.

Prednisolone: increased risk of GI bleeding and ulceration, prednisolone reduces plasma salicylate concentration.

Spironolactone: antagonism of diuretic effect.

Valproic acid: enhancement of effect of valproic acid.

*Warfarin: risk of bleeding due to antiplatelet effect.

Notes:

- Give with or after food.
- Use in treatment of acute or chronic rheumatic fever, juvenile arthritis, Kawasaki disease
- Do not use acetylsalicylic acid in children who have or who are recovering from chickenpox (varicella), influenza, acute febrile illness or flu symptoms due to the rare association with Reye's syndrome. During treatment with acetylsalicylic acid, changes in behaviour may be an early sign of Reye's syndrome. Patients and caregivers should be instructed to contact the health-care provider if these symptoms develop.

Adalimumab

ATC code: L04AB04

Injection, 40 mg/0.4 mL, LOU 6

Indications and dose

Paediatric

Polyarticular juvenile idiopathic arthritis (initiated by a specialist), by SC injection:

Child 2–17 years (body weight 10–29 kg): 20 mg every 2 weeks, review treatment if no response withing 12 weeks.

Child 2–17 years (body weight 30 kg and above): 40 mg every 2 weeks, review treatment if no response within 12 weeks.

Contraindications: Moderate or severe heart failure, severe infection

Precautions: Children should be brought up to date with current immunisation schedule before initiating therapy, demyelinating disorders (risk of exacerbation), development of malignancy, do not initiate until active infections are controlled (discontinue if new serious infection develops), HBV—monitor for active infection, history of malignancy, mild heart failure (discontinue if symptoms develop or worsen), predisposition to infection

Active TB should be treated with standard treatment for at least 2 months before starting adalimumab. Patients who have previously received adequate treatment for TB can start adalimumab but should be monitored every 3 months for possible recurrence. In patients without active TB but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting adalimumab. In patients at high risk of TB who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with adalimumab.

Conception and contraception: Manufacturer advises effective contraception required during treatment and for at least 5 months after last dose.

Pregnancy: Avoid.

Breastfeeding: Avoid, manufacturer advises avoid for at least 5 months after last dose.

Adverse effects: Agranulocytosis, alopecia, anaemia, anxiety, arrhythmias, arterial occlusion. asthma, broken nails, chest pain, coagulation disorder. connective tissue disorders, cough, dehydration. depression, dyspnoea, electrolyte imbalance, embolism and thrombosis, eye inflammation, fever, flushing, GI discomfort, GI disorders, haemorrhage, headaches, healing impaired, hyperglycaemia, hypersensitivity, hypertension, increased risk of infection, insomnia, leucocytosis, leucopenia, mood altered, muscle spasms, musculoskeletal pain, nausea, neoplasms, nerve disorders. neutropenia, oedema, renal impairment, seasonal allergy, sensation abnormal, sepsis, skin reactions, sweat changes, thrombocytopenia, vasculitis, vertigo, vision disorders, vomiting, Aortic aneurysm, congestive heart failure. demyelinating disorders, dysphagia, erectile dysfunction. gallbladder disorders, hearing impairment, hepatic disorders, inflammation, lupus erythematosus. meningitis viral, MI, nocturia. pancreatitis, respiratory disorders, rhabdomyolysis, sarcoidosis, solid organ neoplasm, stroke, tremor, Cardiac arrest, pancytopenia, SJS.

Associated with infections, sometimes severe, including TB, septicaemia, and hepatitis B reactivation.

Interactions with other medicines: Etanercept, Infliximab, Abatacept, Anakinra

Notes:

- Need to screen for TB, HIV and hepatitis viruses. Where possible, vaccinate prior to use
- Pre-treatment screening: TB Patients should be evaluated for TB before treatment.
- Monitoring requirements: Manufacturer advises monitor for infection before, during, and for 4 months after treatment. Manufacturer advises monitor for non-melanoma skin cancer before and during treatment, especially in patients with a history of PUVA treatment for psoriasis or extensive immunosuppressant therapy. For uveitis, manufacturer advises patients should be assessed for pre-existing or developing central demyelinating disorders before and at regular intervals during treatment.
- Patient and caregiver advice: An alert card should be provided.
- When used to treat hidradenitis suppurativa, patients and their caregivers should be advised to use a daily topical antiseptic wash on lesions during treatment with adalimumab.
- TB patients and their caregivers should be advised to seek medical attention if symptoms suggestive of TB (e.g., persistent cough, weight loss, or, and fever) develop.
- Blood disorders Patients and their caregivers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

Etanercept

ATC code: L04AB01

Injection, 25 mg, 50 mg, LOU 6

Indications and dose

Paediatric

Polyarthritis in children who have had an inadequate response to methotrexate or who cannot tolerate it. Extended oligoarthritis in children who have had an inadequate response to methotrexate or who cannot tolerate it, by SC injection:

Child 2–17 years: 400 micrograms/kg twice weekly (max. per dose 25 mg), to be given at an interval of 3—4 days between doses, alternatively 800 micrograms/kg once weekly (max. per dose 50 mg), consider discontinuation if no response after 4 months after 4 months

Contraindications, Precautions, Conception and contraception, Pregnancy, Breastfeeding, Hepatic impairment, Adverse effects, Interactions with other medicines and notes: *See etanercept, 28.2*

Methotrexate

ATC code: L01BA01

Tablet, 2.5 mg (as sodium salt), LOU 4

Injection prefilled syringe 10 mg/mL (0.4 mL), 25 mg/mL (0.4 mL), LOU 4

Indications and dose

Paediatric

Juvenile idiopathic arthritis, Juvenile dermatomyositis, Vasculitis, Uveitis, SLE, Localised scleroderma, Sarcoidosis, oral, or by SC injection, or by IM injection:

Child: Initially 10–15 mg/m2 once weekly, then increased if necessary up to 25 mg/m2 once weekly

Contraindications, Precautions, Conception and contraception, Pregnancy, Breastfeeding, Hepatic impairment, Renal impairment, Adverse effects, Interactions with other medicines and notes: *See methotrexate, 28.2*

Rituximab

ATC code: L01XC02

Injection (IV), 10 mg/mL 10 mL, 50 mL, LOU 6

Indications and dose

Paediatric

Indicated in combination with glucocorticoids for children aged ≥2 years with granulomatosis with polyangiitis and for microscopic polyangiitis, IV Infusion:

Induction: 375 mg/m2 IV weekly for 4 weeks

Before first infusion, administer methylprednisolone 30 mg/kg IV (not to exceed 1g/day) Daily for 3 days

Following methylprednisolone IV, continue oral corticosteroids per clinical practice

Follow up treatment of patients who achieve disease control with induction treatment

250 mg/m2 IV x2 doses separated by 2 weeks, THEN

250 mg/m2 IV every 6months thereafter based on clinical evaluation

If induction treatment of active disease was with a rituximab product, initiate follow up treatment with rituximab within 24 weeks, but no sooner than 16 weeks after last induction infusion based on clinical evaluation

If induction treatment of active disease was with other standard of care immunosuppressants, initiate rituximab follow up treatment within the 4 week period following achievement of disease control

Note: Rituximab is not indicated for polyarticular juvenile idiopathic arthritis

Contraindications, Precautions, Conception and contraception, Pregnancy, Breastfeeding, Hepatic impairment, Renal impairment, Adverse effects, Interactions with other medicines and notes: *See Rituximab, 28.2*

Tocilizumab

ATC code: L04AC07

Injection (solution for IV), 20 mg/0.4 mL, LOU 6

Injection, single use prefilled syringe for subcutaneous injection, 162mg/0.9mL, LOU 6

Indications and dose

Paediatric

Active systemic juvenile idiopathic arthritis (in combination with methotrexate or alone if methotrexate inappropriate, in children who have had an inadequate response to NSAIMs and systemic corticosteroids),

By IV infusion:

Child 2–17 years (body weight up to 30 kg): 12 mg/kg every 2 weeks, for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count—consult product literature, review treatment if no improvement within 6 week.

Child 2–17 years (body weight 30 kg and above): 8 mg/kg every 2 weeks, for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count—consult product literature, review treatment if no improvement within 6 weeks

By SC Injection:

≥2 years (<30 kg): 162 mg every 2weeks

≥2 years (≥30 kg): 162 mg weekly

Polyarticular juvenile idiopathic arthritis [in combination with methotrexate or alone if methotrexate inappropriate, in children who have had an inadequate response to methotrexate],

By IV infusion:

Child 2–17 years (body weight up to 30 kg): 10 mg/kg every 4 weeks, for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count—consult product literature, review treatment if no improvement within 12 weeks Child 2–17 years (body weight 30 kg and above): 8 mg/kg every 4 weeks, for dose adjustments in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count—consult product literature, review treatment if no improvement within 12 weeks

By SC Injection:

≥2 years (<30 kg): 162 mg every 3 weeks

≥2 years (≥30 kg): 162 mg every 2 weeks

Contraindications, Precautions, Conception and contraception, Pregnancy, Breastfeeding, Hepatic impairment, Renal impairment, Adverse effects, Interactions with other medicines and notes: *See tocilizumab, 28.2.2*

Triamcinolone

ATC code: S01BA05

Injection (suspension), 40mg/1mL amp (as acetonide or hexacetonide), LOU5

Indications and dose

Paediatric

Rheumatic and Arthritic Disorders, IM:

Neonates: Not for use in neonates (contains benzyl alcohol);

6-12 years: 0.03-0.2 mg/kg every 1-7 days

>12 years: 60 mg every 6 weeks; may be supplemented by additional 20-100 mg as required (PRN)

Contraindications, Precautions, Adverse effects, Interaction with other medicines, Notes:
See Section 22.2

29. Medicines For Osteoporosis

Alendronic Acid (Alendronate)

ATC code: M05BB03

Tablet, 70 mg, LOU 4

Indications and dose

Adult

Postmenopausal osteoporosis, female:
70 mg once weekly

Osteoporosis in men, male: 70 mg once weekly

Prevention and treatment of corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy female:
70 mg once weekly

Paediatric

Osteogenesis Imperfecta, Bone manifestations in Gaucher's disease, oral:

Child over 2 years:

Child ≤30kg: 35 mg once weekly

Child 30 to <40kg: 35 or 70mg once weekly

Child ≥40kg: 70mg once weekly

Contraindications Abnormalities of oesophagus, hypocalcaemia, other factors which delay emptying (e.g., stricture or achalasia)

Precautions: Active GI bleeding, atypical femoral fractures, duodenitis, dysphagia, exclude other causes of osteoporosis, gastritis, history (within 1 year) of ulcers, surgery of the upper GIT, symptomatic oesophageal disease, ulcers, upper GI disorders

Renal impairment: Avoid if eGFR less than 35 mL/min/1.73 m2.

Pregnancy: Avoid. Foetal risk cannot be ruled out

Breastfeeding: Infant risk cannot be ruled out. Weigh the risk against the benefits.

Adverse effects: GI disorders, joint swelling, vertigo, Haemorrhage, Femoral stress fracture, oropharyngeal, ulceration, photosensitivity reaction, SCARs

Severe oesophageal reactions (oesophagitis, oesophageal ulcers, oesophageal stricture and oesophageal erosions) have been reported, patients should be advised to stop taking the tablets and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain.

Interactions with other medicines: Antacids, calcium, or vitamin supplements

Notes:

- Monitoring requirements: Correct disturbances of calcium and mineral metabolism (e.g., vitamin-D deficiency, hypocalcaemia) before starting treatment. Monitor serum-calcium concentration during treatment.
- Directions for administration: Tablets should be swallowed whole and oral solution should be swallowed as a single 100 mL dose. Doses should be taken with plenty of water while sitting or standing, on an empty stomach at least 30 minutes before breakfast (or another oral medicine), patient should stand or sit upright for at least 30 minutes after administration.
- Patient and Caregiver advice: Patients or their Caregivers should be given advice on how to administer alendronic acid tablets and oral solution. Oesophageal reactions Patients (or their Caregivers) should be advised to stop taking alendronic acid and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain.

Zoledronic Acid

ATC code: M05BA08

Injection 5 mg (100 mL), LOU 5

Indications and dose

Adult

Paget's disease of bone (specialist use only), by IV infusion: 5 mg for 1 dose; at least 500 mg elemental calcium twice daily (with vitamin D) for at least 10 days is recommended following infusion.

Osteoporosis (including corticosteroid-induced osteoporosis) in men and postmenopausal women, by IV infusion: 5 mg once yearly as a single dose; in patients with a recent low-trauma hip fracture, the dose should be given at least 2 weeks after hip fracture repair; before first infusion give 50 000–125 000 units of vitamin D.

Dose adjustment for the 5mg in 100ml Zoledronic acid

CrCl > 35mL/min: No dose adjustment required.

CrCl < 35mL/min: Contraindicated.

Paediatric

Primary osteoporosis (including osteogenesis imperfecta, fibrous dysplasia), secondary osteoporosis associated with chronic diseases (e.g., glucocorticoid-induced osteoporosis), immobility induced osteoporosis in cerebral palsy, Duchenne muscular dystrophy, spinal cord injury, hypercalcemic disorders, IV infusion:

Children and adolescents: 0.025mg/kg every 6 months

Note:

- Various dosing schedules have been studied; Must be used under specialist advise.

» All children/young people should receive a prescription for oral calcium supplements for one week after their first infusion. For subsequent infusions consider regular calcium and vitamin D for 7 days if hypocalcaemia with previous bisphosphonate infusions. Treat vitamin deficiency while ensuring that calcium intake is adequate and for those with poor nutritional state suggestive of suboptimal dietary calcium consider supplementary calcium.

Renal impairment: Avoid in Paget's disease, treatment of postmenopausal osteoporosis and osteoporosis in men if eGFR less than 35 mL/min/1.73 m2.

Dose adjustments as described under dosing.

For Contraindications, Precautions, use in Hepatic impairment, Pregnancy, Breastfeeding, Adverse effects, Interactions with other medicines and notes, *See: Zoledronic acid, section 9.2.5*

30. Medicines For Wound Care

B-Sitosterol

ATC code: D04AX

Ointment, 0.25% w/w (30 g), LOU 2

Indications and dose

Adult and paediatric

Burns or scald wounds, topical use: Apply a thin layer directly onto burn or wounds every 4–6 hours

Adverse effects: None

Contraindications: Hypersensitivity to one of the components, pregnancy, breastfeeding, patients with sitosterolemia

Collagenase Clostridiopeptidase a + Proteases

ATC code: D11AX57

Ointment, 1.2 units + 0.24 units (15 g), LOU 2

Indications and dose

Adult and paediatric

Promote debridement of necrotic tissue in severe burns and dermal ulcers, including decubitus ulcers, topical: Apply once daily (or more frequently if the dressing becomes soiled) until debridement of necrotic tissue is complete and granulation tissue is well established. If infection is present, apply an appropriate topical antibiotic prior to the application of collagenase. If the infection persists despite treatment, discontinue use of collagenase until remission of the infection.

Administration:

Prior to application, cleanse the wound of debris and digested material by gently rubbing with a gauze pad saturated with normal saline or another compatible cleansing solution followed by a normal saline rinse, detergents and antiseptics or soaks containing heavy metal ions (e.g., mercury, silver) may decrease the enzymatic activity of collagenase and should be avoided

The enzymatic activity is optimal at a pH range of 6 to 8, precautions should be taken to ensure optimal pH at the application site.

Apply collagenase directly to the wound or to a sterile gauze pad and then apply to the wound and secure. Application should be carefully confined to the area of the wound, transient erythema may occur in surrounding tissue when application is not confined to the wound.

Contraindications: Local or systemic hypersensitivity to collagenase or any component of the formulation.

Adverse effects: Application site burning, application site irritation, application site pain, Hypersensitivity reactions.

Note:

» Use for chemical debridement of wounds

Distilled Water

ATC code: V07AB

Liquid, 500 mL, LOU 2

Indications and dose

Adult and paediatric

Use for cleaning wounds once daily

Adverse effects: None

Notes:

» Discard the bottle after opening

Human Epidermal Growth Factor (Recombinant)

ATC code: D03

Gel (water-based), 60 micrograms (15 g), LOU 4

Indications and dose

Adult and paediatric

Assists in epithelialisation of wounds and growth of epidermis, topical: Once a day

Human Platelet Derived Growth Factor (Recombinant)

ATC code: D03AX06

Gel (water-based), 100 micrograms (15 g), LOU 4

Indications and dose

Adult and paediatric

Use in diabetic patients to granulate necrotic tissue, topical: Once daily

Contraindications: Known neoplasm(s)

Adverse effects: erythema, malignancy

Metronidazole

ATC code: D06BX01

Gel, 0.75% or 0.80%, LOU 4

Indications and dose

Adult and paediatric

Acute inflammatory exacerbation of rosacea: Apply thinly twice daily for 8 weeks

Inflammatory papules and pustules of rosacea: Apply twice daily for 6 weeks (longer if necessary)

Malodorous fungating tumours and malodorous gravitational and decubitus ulcers: Apply 1–2 times a day to a clean wound and cover with non-adherent dressing

Contraindications/Precautions: Hypersensitivity to this product or nitroimidazoles, parabens. Hepatic disease, blood dyscrasias, children. Watery eyes, metallic taste

in mouth, numbness and paraesthesias or any other Adverse effects may occur and need to be reported. May cross-react in patients with allergy to oral forms.

Adverse effects: Dryness, itching, burning, stinging

Notes:

» **Patient information:** Topical skin products are not for intravaginal therapy. Drugs used in Skin Disorders and are for external use only, do not use skin products near the eyes, nose, or mouth. Avoid exposure to strong sunlight or UV light

Papain + Urea (Papain-Urea Topical)

ATC code: D03BA02

Ointment, 521,700 IU + 100 mg (15 g), LOU 4

Indications and dose

Adult and paediatric

Enzymatic debridement of large burn wounds, bed sores: Apply ointment directly to the wound, cover with appropriate dressing, and secure in place; if possible, change the dressing 1 to 2 times per day

Contraindications: Pregnancy, lactating mothers

Adverse effects: allergic reactions like skin rash, itching or hives, swelling of the face, lips, or tongue, breathing problems, continued swelling, burning, itching, stinging, or pain

Note:

» Do not use hydrogen peroxide or medicines that contain heavy metals such as lead, silver and mercury

Silver Ions

ATC code: D08AL30

Solution, 0.01% (100 mL), 0.01% (250 mL), LOU 4

Indications and dose

Adult and paediatric

Advanced wound care: Antimicrobial dressings containing silver should be used only when infection is suspected as a result of clinical signs or symptoms; apply once daily

Contraindications: Hypersensitivity

Adverse effects: fever, skin rash, sweating, redness or pain

Notes:

» Silver-based wound dressings are often used to prepare the wound for healing. Silver is a broad-spectrum antimicrobial agent that controls yeast, mold, and bacteria, including MRSA and vancomycin-resistant *enterococci*, when it is provided at an appropriate concentration. It kills microbes on contact through multiple mechanisms of action, such as inhibiting cellular respiration, denaturing nucleic acids, and altering cellular membrane permeability. Silver has low mammalian cell toxicity. It is now known to have potent anti-inflammatory properties, which are dependent on the delivery system. It may be used to maintain a microbe-free, moist wound healing environment.

Silver Sulphadiazine

ATC code: D06BA51

Cream, 1% w/w 50 g, 250 g, LOU 2

Indications and dose

Adult and paediatric

Minor burns: Apply once daily or twice daily if exudative

Contraindications/Precautions: Hypersensitive to sulphonamides, pregnancy [C, X (near term)], breastfeeding and neonates. Hepatic, renal impairment, G-6PD deficiency. Owing to the association of sulfonamides with severe blood and skin disorders, treatment should be stopped immediately if blood disorders or rashes develop.

Adverse effects: Allergic reactions, argyria (following treatment of large areas of skin or prolonged use), burning, itching, leucopenia, rashes

Interactions with other medicines: Decreases effects of collagenase, papain, trypsin

Zinc Hyaluronate (Zinc-Hyaluronan)

ATC code: D02AB

Gel (water-based), 15 g, LOU 2

Indications and dose

Adult and paediatric

Assists in epithelialization of wounds, topical: Apply once or twice after showering

Contraindications: allergy to hyaluronate

Adverse Reactions:

In some case local hypersensitivity (allergic reaction) may emerge.
The following symptoms may occasionally occur at the beginning of use: redness, mild transient stinging or burning sensations, and local pain.

31. Medicines For Correcting Water, Electrolyte & Acid-Base Disturbances

31.1. *Oral*

Calcium Carbonate

ATC code A12AA04

Tablet, 500 mg, LOU 4

Indications and dose

Adult

Adjunctive therapy in osteoporosis, oral: 2 to 3 tablets daily.

Prevention and treatment of calcium deficiency, oral: Adult 2 to 3 tablets daily.

Phosphate binder: Dose as required by the individual patient depending on serum phosphate level.

Paediatric

Phosphate binding in renal failure and hyperphosphataemia, Oral:

Child 1–11 months: 120 mg 3–4 times a day, dose to be adjusted as necessary, to be taken with feeds

Child 1–5 years: 300 mg 3–4 times a day, dose to be adjusted as necessary, to be taken prior to or with meals

Child 6–11 years: 600 mg 3–4 times a day, dose to be adjusted as necessary, to be taken prior to or with meals

Child 12–17 years: 1.25 g 3–4 times a day, dose to be adjusted as necessary, to be taken prior to or with meals

Calcium deficiency, Oral:

Neonate: 0.25 mmol/kg 4 times a day, adjusted according to response.

Child 1 month–4 years: 0.25 mmol/kg 4 times a day, adjusted according to response

Child 5–11 years: 0.2 mmol/kg 4 times a day, adjusted according to response

Child 12–17 years: 10 mmol 4 times a day, adjusted according to response

Contraindications: Diseases and/or conditions resulting in hypercalcaemia and/or hypercalciuria, for example in hyperparathyroidism, vitamin D overdosage, decalcifying tumours such as plasmacytoma and skeletal metastases, in severe renal failure untreated by renal dialysis and in osteoporosis due to immobilisation. Renal calculi (nephrolithiasis)

Adverse effects: Hypercalciuria, Flatulence, GI discomfort, milk-alkali syndrome, skin reactions

Interaction with other medicines:

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Calcium carbonate may interfere with the absorption of concomitantly administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least two hours before, or four to six hours after, oral intake of calcium.

Hypercalcaemia may increase the toxicity of cardiac glycosides during treatment with calcium. Patients should be monitored with regard to ECG and serum calcium levels.

If a bisphosphonate is used concomitantly, this preparation should be administered at least three hours before the intake of calcium carbonate 500 mg Chewable Tablets since GI absorption may be reduced.

The efficacy of levothyroxine can be reduced by the concurrent use of calcium, due to decreased levothyroxine absorption. Administration of calcium and levothyroxine should be separated by at least four hours.

The absorption of quinolone antibiotics may be impaired if administered concomitantly with calcium. Quinolone antibiotics should be taken two hours before or after intake of calcium.

Calcium salts may decrease the absorption of iron, zinc and strontium ranelate. Consequently, iron, zinc or strontium ranelate preparations should be taken two hours before or after calcium carbonate.

Notes:

- In renal insufficiency the tablets should be given only under controlled conditions for hyperphosphataemia. Caution should be exercised in patients with a history of renal calculi.
- Monitoring is especially important in patients on concomitant treatment with cardiac glycosides or diuretics.
- During high dose therapy and especially during concomitant treatment with vitamin D and/or medications or nutrients (such as milk) containing calcium, there is a risk of hypercalcaemia and milk-alkali syndrome (hypercalcaemia, alkalosis and renal impairment) with subsequent kidney function impairment. In these patients, serum calcium levels should be monitored and renal function should be monitored.

Calcium Carbonate + Vitamin D

ATC Code: A12AX

Tablet, minimum calcium 1000mg + 600IU of vitamin D, LOU 4

Indications and dose

Adult

Prevention and treatment of calcium and vitamin D deficiency especially in the elderly, oral: Dosed according to the deficit or daily maintenance requirements.

Consult product literature and refer to guidance below:

Daily dietary reference intake for calcium and vitamin D:

19-50 years: 1000 mg + 600 IU daily

≥51-70 years (males): 1000 mg + 600 IU

≥51 years (females): 1200 mg + 600 IU

≥70 years (males): 1200 mg + 800 IU

Pregnancy and breastfeeding: 1000mg + 600IU

Osteoporosis prevention in adults ≥50 years, oral: Vitamin D intake may need to be increased to 800-1000 mg.

Paediatric

Not recommended in children under 12 years. Dosed according to the deficient or daily maintenance requirements (consult product literature).

Precautions: Refer to respective monographs for calcium and vitamin D

Contraindications: Hypersensitivity to the active substance or to any of the excipients, hypercalcaemia, bone metastases or other malignant bone disease, sarcoidosis; primary hyperparathyroidism and vitamin D overdosage, Severe renal failure, Hypercalcemia, Hypervitaminosis D. Relative contra-indications are osteoporosis due to prolonged immobilisation, renal stones, severe hypercalciuria.

Pregnancy and Breastfeeding: Requirements for calcium and vitamin D are increased.

Adverse effects: Hypersensitivity reactions including pruritus, wheezing, urticaria and oropharyngeal swelling. Mild gastro-intestinal disturbances, such as constipation, flatulence, nausea, gastric pain, diarrhea, occasional skin rash, Hypercalciuria, and in rare cases hypercalcaemia have been seen with long term treatment at high dosages.

Interactions with other medicines (*indicates serious): *baloxavir marboxil, cabotegravir, deferiprone, delafloxacin, omadacycline, rifampin, rilpivirine, sarecycline, sodium sulfate/magnesium sulfate/potassium chloride

Notes:

- High risk for vitamin D deficiency is observed in those ≥50 years, consistently wearing sunscreen.
- Food may increase absorption.
- Use I.V 10% calcium gluconate in children to rectify symptomatic hypocalcaemia.
- Use caution administering calcium supplements to patients with a history of kidney stones.

Calcium Polystyrene Sulphonate

ATC code: V03AE01

Powder for oral/rectal suspension, 15g sachets, LOU4

Indications and dose

Adult

Treatment of hyperkalaemia, oral: 15 g three or four times a day; given as a suspension in a small amount of water (3-4mL per gram of resin) or, for greater palatability, in syrup (but not fruit juices which contain potassium)

By rectal route (reserved for vomiting patient or those with upper gastrointestinal tract problems): 30 g resin in 150 ml of water or 10% dextrose, as a daily retention enema (should be retained for at least nine hours, if possible, then colon irrigated to remove resin).

Paediatric

Treatment of hyperkalaemia, oral:

Neonate: Calcium polystyrene should not be given by oral route

Child: 1g/kg body weight daily in divided doses for acute hyperkalemia. Maintenance: 0.5g/kg body weight daily in divided doses

By rectal:

Neonate: 0.5g-1g/kg, diluted as for adult, with adequate irrigation to ensure recovery of the resin.

Child: When refused orally, give oral dose rectally, diluting in same ratio as for adults (1g/5ml of 10% dextrose); irrigate adequately to ensure recovery of resin

Contraindications: Patients with plasma potassium levels below 5 mmol/litre. Conditions associated with hypercalcaemia (e.g., hyperparathyroidism, multiple myeloma, sarcoidosis, or metastatic carcinoma). History of hypersensitivity to polystyrene sulfonate resins. Obstructive bowel disease. Should not be administered orally to neonates and is contraindicated in neonates with reduced gut motility (post-operatively or drug induced). Hypersensitivity to the active substance or to any of the excipients

Precautions:

Gastrointestinal stenosis and ischaemia:

- Gastrointestinal stenosis, intestinal ischemia, and its complications (necrosis and perforation), some of them fatal, were reported in patients treated with polystyrene sulfonate alone or in combination with sorbitol. Concomitant use of sorbitol with polystyrene sulfonate is not recommended.
- Patients should be advised to seek prompt medical advice in case of newly developed severe abdominal pain, nausea and vomiting, stomach distension and rectal bleeding.
- Lesions seen in polystyrene sulfonate-induced gastrointestinal damage may overlap with those seen in inflammatory bowel disease, ischemic colitis, infectious colitis, and microscopic colitis.

Hypokalaemia: The possibility of severe potassium depletion should be considered, and adequate clinical and biochemical control is essential during treatment, especially in patients on digitalis. Administration of the resin should be stopped when the serum potassium falls to 5mmol/litre.

Other electrolyte disturbances: Calcium polystyrene sulfonate is not totally selective for potassium. Hypomagnesaemia and/or hypercalcaemia may occur.

Accordingly, patients should be monitored for all applicable electrolyte disturbances. Serum calcium levels should be estimated at weekly intervals to detect the early development of hypercalcaemia, and the dose of resin adjusted to levels at which hypercalcaemia and hypokalaemia are prevented.

Other risks: In the event of clinically significant constipation, treatment should be discontinued until normal bowel movement has resumed. Magnesium-containing laxatives should not be used.

Pregnancy: There is a limited amount of data for the use of calcium polystyrene sulfonate in pregnant women. It is not recommended during pregnancy and in woman of childbearing potential not using contraception.

Breastfeeding: There is insufficient information on the excretion of calcium polystyrene sulfonate in human milk. A risk to the newborns/infants cannot be excluded.

Adverse effects: *Common:* Hypokalaemia, hypercalcaemia, hypomagnesaemia, Nausea, vomiting, constipation.*Uncommon*: Decreased appetite, Diarrhoea, gastric irritation, gastrointestinal ulcer, intestinal obstruction. *Rare*: faecal impaction following rectal administration particularly in children and gastrointestinal concretions (bezoars) following oral administration. Gastrointestinal necrosis (colon necrosis), which could lead to intestinal perforation which is sometimes fatal. *Very rare*: Acute bronchitis and/or bronchopneumonia associated with inhalation of particles of calcium polystyrene sulfonate

Interactions with other medicines: Sorbitol (oral or rectal): Concomitant use of Sorbitol with calcium polystyrene sulfonate is not recommended due to cases of intestinal necrosis and other serious gastrointestinal adverse reactions, which may be fatal

To be used with caution with:

- Cation-donating agents: may reduce the potassium binding effectiveness of Calcium Polystyrene Sulfonate.
- Non-absorbable cation-donating antacids and laxatives: There have been reports of systemic alkalosis following concurrent administration of cation-exchange resins and non-absorbable cation-donating antacids and laxatives such as magnesium hydroxide and aluminium carbonate.
- Aluminium hydroxide: Intestinal obstruction due to concretions of aluminium hydroxide has been reported when aluminium hydroxide has been combined with the resin
- Digitalis-like drugs: The toxic effects of digitalis on the heart, especially various ventricular arrhythmias, and AV nodal dissociation, are likely to be exaggerated if hypokalaemia and/or hypercalcaemia are allowed to develop
- Lithium: Possible decrease of lithium absorption.
- Levothyroxine: Possible decrease of levothyroxine absorption.

Note:

- The dosage recommendations are a guide only; the precise requirements should be determined based on regular serum electrolyte levels.
- For neonates: Calcium polystyrene should not be given by oral route.
- Should be administered at least 3 hours before or 3 hours after other oral medications. For patients with gastroparesis, a 6-hour separation should be considered.
- The rectal route may be used simultaneously with the oral route for more rapid initial results.
- Monitor all applicable electrolyte disturbances.

Magnesium Chloride

ATC code: A12CC01

Tablet, 71.5 mg (containing calcium as carbonate 119 mg per tablet), LOU 4

Indications and dose

Adult

Correction and prevention of hypomagnesemia, oral: 54–483 mg/day in divided doses.

The recommended daily allowance (RDA) of magnesium is 4.5 mg/kg which is a total daily allowance of 350–400 mg for adult men and 280–300 mg for adult women. During pregnancy, the RDA is 300 mg and during breastfeeding the RDA is 355 mg.

Paediatric

Child and adolescent: 2–10 mEq/day (203mg to 1015mg of magnesium chloride per day in divided doses)

The usual recommended paediatric maintenance intake of magnesium ranges from 0.2–0.6 mEq/kg/day. The dose of magnesium may also be based on the caloric intake, on that basis, 3–10 mEq/day of magnesium is needed, maximum maintenance dose: 8–16 mEq/day

Adverse reactions: GI, Diarrhea (excessive oral doses)

Oral rehydration salts (ORS)

ATC code: A07CA,

Powder for oral liquid sachet (WHO low-osmolarity formula) powder for dilution in 500 mL, LOU 1

Indications and dose

Adult

Fluid and electrolyte loss in acute diarrhoea, oral: 200–400 mL solution after every loose motion

Paediatric

WHO Recommends Plans A, B and C, see below.

Plan A: no dehydration Nutritional advice, increased fluid intake (e.g., unsalted soup, unsalted rice water, yoghurt or plain water), at least one fluid that normally contains salt (e.g., ORS solution, salted drinks including salted rice water and vegetable or chicken soup with salt) and zinc supplementation at home are usually sufficient. The aim is to give as much nutrient-rich food as the child will accept. Breastfeeding should always be continued to reduce the risk of diminishing supply. Give as much fluid as the child wants until diarrhoea stops and, as a guide, after each loose stool give:

Child under 2 years: 50–100 mL (a quarter to half a large cup) of fluid,

Child 2–10 years: 100–200 mL (a half to one large cup), older than 10 years as much fluid as the child wants.

Parents should be advised about circumstances in which they should seek further advice.

Plan B: moderate dehydration whatever the child's age, a 4 hour treatment plan is applied to avoid short-term problems. It is recommended that parents are shown how to give approximately 75 mL/kg of oral rehydration solution over a 4 hour period, and it is suggested that parents should be watched to see how they cope at the beginning of the treatment. A larger amount of solution (up to 20 mL/kg/hour and maximum 750 mL/hour) can be given if the child continues to have frequent stools or if the child wants more than the estimated amount of ORS solution, and there are no signs of overhydration (e.g., oedematous eyelids). In case of vomiting, rehydration must be discontinued for 10 minutes and then resumed at a slower rate. In younger children, breastfeeding should be continued on demand and the mother should be encouraged to do so, older children should receive milk and nutritious food as normal after completing the 4 hours of oral rehydration. The child's status must be reassessed after 4 hours to decide on the most appropriate subsequent treatment. If signs of dehydration worsen, shift to treatment

Plan C: and if the child develops signs of severe dehydration, IV rehydration should be started as per treatment plan C. Zinc supplementation should begin as soon as the child can eat and has completed 4 hours of rehydration. Oral rehydration solution should continue to be offered once dehydration has been controlled, for as long as the child continues to have diarrhoea. severe dehydration Hospitalization is necessary, but the most urgent priority is to start rehydration. The preferred treatment for children with severe dehydration is rapid IV rehydration. In hospital (or elsewhere), if the child can drink, oral rehydration solution should be given during the IV rehydration (20 mL/kg/hour oral before infusion, then 5 mL/kg/hour oral during IV rehydration). For IV rehydration, it is recommended that compound solution of sodium lactate (or, if this is unavailable, sodium chloride 0.9% IV infusion) is administered at a rate adapted to the child's age.

IV rehydration using compound sodium lactate solution or sodium chloride 0.9% infusion

IV:

Infant: 30 mL/kg over 1 hour, then 14 mL/kg/hour for 5 hours.

Child: 30 mL/kg over 30 minutes, then 28 mL/kg/hour for 2.5 hours.

If the IV route is unavailable, a nasogastric tube is also suitable for administering oral rehydration solution.

Nasogastric rehydration using oral rehydration solution

Nasogastric tube:

Infant or Child: 20 mL/kg/hour for 6 hours (total 120 mL/kg).

If the child vomits, the rate of administration of the oral solution should be reduced. Reassess the child's status after 3 hours (6 hours for infants) and continue treatment as appropriate with plan A, B or C.
Precautions: Renal impairment.

Adverse effects: Vomiting (may indicate too rapid administration), hypernatraemia and hyperkalaemia (may result from overdose in renal impairment or administration of too concentrated a solution).

Oral rehydration salts + Zinc sulphate

ATC code: ORS A07CA, Zinc sulphate A12CB01

Co-pack (4 sachets + 10tablets) powder for oral liquid in sachet to make 500 mL + 20 mg tablet (dispersible)

Indications and dose

See under Oral rehydration for ORS indications and dose

Paediatric

Zinc Sulphate: Adjunct to oral rehydration therapy in acute diarrhoea, oral:

Infant under 6 months: 10 mg (elemental zinc) daily for 10–14 days,

Child 6 months - 5 years: 20 mg (elemental zinc) daily for 10–14 days.

Administration: Zinc sulphate tablets may be dispersed in breastmilk, in oral rehydration solution, or in water on a small spoon, older children may chew the tablets or swallow them with water.

Precautions: acute renal failure (may accumulate)

Renal impairment Accumulation may occur in acute renal failure.

Pregnancy Crosses placenta, risk theoretically minimal, but no information available.

Breastfeeding Present in milk, risk theoretically minimal, but no information available.

Adverse effects: abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, gastritis, irritability, headache, lethargy.

Interactions with other medicines: Zinc may inhibit the absorption of copper

Tetracycline Antibacterials: Zinc may reduce the absorption of concurrently administered tetracyclines, also the absorption of zinc may be reduced by tetracyclines, when both are being given an interval of at least three hours should be allowed.

Quinolone Antibacterials: Zinc may reduce the absorption of quinolones, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin.

Calcium Salts: The absorption of zinc may be reduced by calcium salts.

Iron: The absorption of zinc may be reduced by oral iron, also the absorption of oral iron may be reduced by zinc.

Penicillamine: The absorption of zinc may be reduced by penicillamine, also the absorption of penicillamine may be reduced by zinc.

Trientine: The absorption of zinc may be reduced by trientine, also the absorption of trientine may be reduced by zinc.

Potassium Chloride

ATC code: A12BA01

Tablet (e/r), 600 mg, LOU 4

Indications and dose

Adult

Prevention of hypokalemia, oral: 20–50 mmol daily after meals (possibly lower doses in the elderly).

Potassium depletion, oral: adult, 40–100 mmol daily in divided doses after meals, adjust the dose according to severity of deficiency and any continuing loss of potassium.

Paediatric

Hypokalaemia, oral: 0.5 to 0.75 mEq/kg IV infused over 1 to 2 hours, then reassess

3 to 8 mEq/kg/day, divided 1 to 5 times per day depending on tolerability and dose, start at lower dose and adjust based on serum potassium concentrations

Contraindications: Anticholinergic agents, GI tract passage restrictions or delay may inhibit extended-release tablet passage

Cardiac patients with esophageal compression, extended-release tablets may cause esophageal ulceration due to enlarged left atrium

Concomitant pharmacologic agents in sufficient doses exerting anticholinergic effects, GI tract passage restrictions or delay may inhibit extended-release tablet passage

Structural or pathological conditions causing GI tract passage restrictions or delay, may inhibit extended-release tablet passage

Hyperkalemia, risk of cardiac arrest

Precautions:

Acidosis or alkalosis patients, especially cardiac and renal disease, serum potassium levels may not represent total body potassium

Acidosis, systemic, risk of hyperkalemia

Adrenal insufficiency, risk of hyperkalemia

Burn patients, risk of hyperkalemia due to extensive tissue breakdown

Concomitant use of ACEI, inhibits aldosterone production resulting in potassium retention

Concomitant use of potassium-sparing diuretics, risk of hyperkalemia

Dehydration, acute, risk of hyperkalemia

GI ulcerative and/or stenotic lesions, associated with solid oral dosage forms due to high local concentrations of potassium near the GI wall

Metabolic acidosis, hypokalemia should be treated with an alkalinizing potassium salt

Potassium excretion mechanism, impaired, may cause potentially fatal asymptomatic hyperkalemia and cardiac arrest

Tissue breakdown, extensive, risk of hyperkalemia

Renal failure: chronic, risk of hyperkalemia.

Pregnancy: Foetal risk cannot be ruled out.

Breastfeeding: Infant risk cannot be ruled out.

Adverse effects: Common: GI, Diarrhea, Flatulence, Nausea, Vomiting. Serious: Cardiovascular: Cardiac arrest, ECG abnormal, Endocrine metabolic, Hyperkalemia, GI: Abdominal pain, GI ulcer

Interaction with other medicines: Contraindicated: Amantadine, Atropine, Belladonna, Belladonna Alkaloids, Benztropine, Biperiden, Clidinium, Darifenacin, Dicyclomine, Eplerenone, Fesoterodine, Glycopyrrolate, Hyoscyamine, Methscopolamine, Oxybutynin, Procyclidine, Scopolamine, Solifenacin, Tolterodine, Trihexyphenidyl, Trospium.

Major: Alacepril, Amiloride, Benazepril, Canrenoate, Captopril, Cilazapril, Delapril, Fosinopril, Imidapril, Indomethacin, Lisinopril, Moexipril, Pentopril, Perindopril, Quinapril, Ramipril, Spirapril, Spironolactone, Temocapril, Trandolapril, Triamterene, Zofenopril Licorice

Rehydration Solution For Malnutrition

ATC code: A07CA01

Powder for oral liquid (to make 1 L), sachet (42 g), WHO formula, LOU 4

Powder for oral dilution to make 1 L (42 g) (WHO formula), LOU 4

Indications and dose

Paediatric

Rehydration and correction of electrolyte derangements in SAM in children

It is difficult to estimate dehydration status in a severely malnourished child using clinical signs alone. Assume all children with watery diarrhoea may have dehydration and give: ReSoMal 5 mL/kg every 30 min. for two hours, orally or by nasogastric tube, then 5–10 mL/kg/h for next 4–10 hours: the exact amount to be given should be determined by how much the child wants, and stool loss and vomiting. Replace the ReSoMal doses at 4, 6, 8 and 10 hours with F-75 if rehydration is continuing at these times, then continue feeding starter F-75.

Prevention:

To prevent dehydration when a child has continuing watery diarrhoea:

- keep feeding with starter F-75
- replace approximate volume of stool losses with ReSoMal. As a guide give 50–100 mL after each watery stool. (Note: it is common for malnourished children to pass many small unformed stools: these should not be confused with profuse watery stools and do not require fluid replacement)
- If the child is breastfed, encourage to continue

Contraindications: Do not administer to patients with

cholera or uncomplicated acute malnutrition: use standard ORS instead.

Precautions: May cause heart failure when administered too rapidly. During treatment, closely monitor the rate of administration to avoid overhydration. Increase in respiratory and pulse rates and appearance or increase of oedema are signs of over rapid rehydration. In this event, stop ReSoMal for one hour then reassess the patient's condition.

Renal impairment: Dose reduction may be necessary, monitor electrolytes carefully.

Hepatic impairment: Dose reduction not necessary.

Interaction with other medicines: There are no known interactions where it is recommended to avoid concomitant use.

Note:

» The standard ORS solution (90 mmol sodium/L) contains too much sodium and too little potassium for severely malnourished children.

Sevelamer

ATC code V03AE02

Tablet, 400 mg, 800 mg, LOU 4

Indications and dose

Adult

Indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis. Used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25-dihydroxy vitamin D3 or one of its analogues to control the development of renal bone disease.

Starting dose, oral: 2.4 g or 4.8 g per day based on clinical needs and serum phosphorus level.

For patients previously on phosphate binders, sevelamer should be given on a gram for gram basis with monitoring of serum phosphorus levels to ensure optimal daily doses.

Titration and maintenance, oral: Serum phosphate levels should be closely monitored and the dose of sevelamer HCl titrated by 0.8 g three times per day (2.4 g/day) increments with the goal of lowering serum phosphate to 1.76 mmol/L (5.5 mg/dL) or less. Serum phosphate should be tested every two to three weeks until a stable serum phosphate level is reached and on a regular basis thereafter.

The dose range may vary between 1 and 5 tablets of 800 mg per meal. The average actual daily dose used in the chronic phase of a one-year clinical study was 7 grams of sevelamer.

Paediatric

No or insufficient experience in children and adolescents therefore its use is not recommended.

Contraindications: Hypersensitivity to sevelamer, Hypophosphataemia, Bowel obstruction

Precautions: Dysphagia and esophageal tablet retention have been reported, including cases requiring hospitalization and intervention. Consider using suspension for patients with a history of swallowing disorders. Bowel obstruction, bleeding GI ulcers, colitis, ulceration, necrosis, and intestinal perforation have been reported. Reevaluate treatment in patients who develop severe GI symptoms.

Vitamin levels: Reductions in folic acid and clotting factors (vitamins D, E, and K)

Adverse effects: Hypersensitivity, Metabolism and nutrition disorders, Acidosis, increased serum chloride levels, Nausea, vomiting, Diarrhoea, dyspepsia, flatulence, upper abdominal pain, constipation, Abdominal pain, intestinal obstruction, ileus/subileus, diverticulitis, intestinal perforation1, GI haemorrhage, intestinal ulceration, GI necrosis, colitis, intestinal mass, Pruritus, rash

Interaction with other medicines:

Ciprofloxacin In interaction studies in healthy volunteers, sevelamer HCl decreased the bioavailability of ciprofloxacin by approximately 50% when co-administered with Sevelamer in a single dose study. Consequently, Sevelamer should not be taken simultaneously with ciprofloxacin.

Anti-arrhythmics and anti-seizure medicinal products Patients taking anti-arrhythmic medicinal products for the control of arrhythmias and anti-seizure medicinal products for the control of seizure disorders were excluded from clinical trials. Caution should be exercised when prescribing sevelamer HCl to patients also taking these medicinal products.

Levothyroxine During post marketing experience, very rare cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients co-administered sevelamer HCl and levothyroxine. Closer monitoring of TSH levels is therefore recommended in patients receiving both medicinal products.

Ciclosporin, mycophenolate mofetil and tacrolimus in transplant patients reduced levels of ciclosporin, mycophenolate mofetil and tacrolimus have been reported in transplant patients when coadministered with sevelamer HCl without any clinical consequences (i.e. graft rejection).

Proton pump inhibitors during post-marketing experience, very rare cases of increased phosphate levels have been reported in patients taking proton pump inhibitors co-administered with sevelamer HCl.

Sodium Acid Phosphate

ATC code: B05XA09

Tablets (effervescent) 1.936 g (equivalent to phosphorous 500 mg), LOU 4

Note: Tablet contains other constituents: sodium bicarbonate and potassium bicarbonate

Indications and dose

Adults

Hypercalcaemia, oral: Up to 6 tablets daily (adjustment being made according to requirements)

Vitamin D resistant hypophosphateaemic osteomalacia, oral: 4–6 tablets daily

Paediatric

Hypercalcaemia, oral:

Children < 5 years: up to 3 tablets daily (adjustment being made according to requirements).

Child ≥5years and adolescents: Up to 6 tablets daily (adjustment being made according to requirements)

Vitamin D resistant rickets, oral:

Children < 5 years: 2–3 tablets daily

Vitamin D resistant hypophosphateaemic osteomalacia, oral:

Child ≥5years and adolescents: 4–6 tablets daily

Contraindications: None

Precautions: Impaired renal function associated with hypercalcaemia

Restricted sodium intake, e.g., congestive cardiac failure, hypertension or pre-eclamptic toxaemia, the sodium and potassium content in the multi-ingredient tablet should be taken into consideration.

In cases of hypercalcaemia associated with impaired renal function and hyperphosphataemia, the main effect of oral phosphate is to bind calcium in the gut and thus reduce calcium absorption.

The effect of oral phosphate on serum phosphate is likely to be minimal, but close monitoring of serum levels is recommended.

Dosage should be adjusted to suit the requirements of individual patients.

Excessive dosage has been reported to produce hypocalcaemia in isolated cases. Particular care should therefore be taken to ensure appropriate dosage in the elderly.

Adverse effects: GI upsets, nausea and diarrhoea

Interaction with other medicines: Concurrent administrations of antacids, containing agents such as aluminium hydroxide, may result in displacement of calcium from binding to oral phosphate, thus reducing efficacy.

Notes:

» Should be dissolved in 1/3 to 1/2 a tumblerful of water and taken orally.

Sodium Citrate + Citric Acid (Shohl's Solution)

ATC code: B05CB02

Oral solution, 500 mg + 334 mg/5 mL (30 mL), LOU 5

Indications and dosage

Adult

Urine alkalinization, prevention of nephrolithiasis and management of metabolic acidosis, oral: 10–30 mL diluted in up to 170 mL water/juice *orally* after meals and at bedtime as needed. Follow with additional water if desired

Paediatric

Urine alkalinization, prevention of nephrolithiasis and management of metabolic acidosis, e.g., in paediatric patients with renal tubulopathy,

Children under 2 years: Based on paediatrician's discretion

Children 2 years and older: 5–15 mL diluted in 30–90 mL of water/juice orally after meals and at bedtime as needed

Follow with additional water if desired

Contraindications: Hypersensitivity to drug or component of the formulation, severe renal impairment, sodium-restricted diet

Precautions: Use with caution in high blood pressure, kidney or liver disease, cardiac failure, toxemia of pregnancy, peripheral/pulmonary edema, shock, or the severely ill.

Do not dilute in tomato juice

Pregnancy and Breastfeeding: Use sodium citrate/ citric acid with caution during pregnancy if benefits outweigh risks.

Adverse effects: Diarrhea, Nausea, Muscle spasms, metabolic alkalosis, Vomiting, Stomach, Fluid retention

Interactions with other medicines: Atazanavir, Dapsone, Digoxin, Doxycycline, Gemifloxacin, Indinavir, Itraconazole, Ketoconazole, Levofloxacin, Minocycline, Moxifloxacin, Ofloxacin, Tetracycline

Sodium Chloride

ATC code: B05XA03

Tablet, 600 g, LOU 4

Indications and dose

Adult

For the treatment and prophylaxis of sodium deficiency, oral:

Prophylaxis 4–8 tablets per day.

Treatment dosage to be adjusted to individual needs up to a maximum of 20 tablets per day in cases of severe salt depletion.

Control of muscle cramps during routine maintenance haemodialysis, oral: 10–16 tablets per dialysis. In some cases of chronic renal salt-wasting up to 20 tablets per day may be required with appropriate fluid intake.

» *Elderly*: No special dosage adjustment.

Paediatric: Dosage should be adjusted to individual needs.

Contraindications: Sodium chloride is contraindicated in any situation where salt retention is undesirable, such as oedema, heart disease, cardiac decompensation and primary or secondary aldosteronism, or where therapy is being given to produce salt and water loss.

Precautions: Use of sodium chloride without adequate water supplementation can produce hypernatraemia. The matrix (ghost) is often eliminated intact and owing to the risk of obstruction Sodium chloride should not be given to patients suffering from Crohn's disease or any other intestinal condition where strictures or diverticula may form.

Adverse effects: No Adverse effects have been reported with sodium chloride at the recommended dosage.

Interactions with other medicines: In hypertensive patients with chronic renal failure sodium chloride may tend to impair the efficacy of antihypertensive drugs.

Note:

- Tablets should be swallowed whole with water (approx. 70 mL per tablet where kidney function is normal to avoid hypernatraemia)
- Tablets should not be chewed.

Sodium Polystyrene Sulphonate

ATC code: V03AE

Powder, 450 mg, LOU 4

Indications and dose

Adult

Hyperkalaemia associated with anuria or severe oliguria and in dialysis patients, Oral: 15 g 3–4 times a day

Paediatric

Hyperkalaemia, oral:

children and infants: An appropriate initial dose is 1 g/kg body weight daily in divided doses, in acute hyperkalaemia.

Dosage may be reduced to 0.5 g/kg of body weight daily in divided doses for maintenance therapy.

The resin is given *orally*, preferably with a drink (not a fruit squash because of the high potassium content) or a little jam or honey.

Note: 1 mEq of potassium per gram of resin is used as the basis for dose calculation

Contraindications: Obstructive bowel disease, In patients with plasma potassium levels below 5 mmol/L, History of hypersensitivity to polystyrene sulfonate resins, Obstructive bowel disease, should not be administered orally to neonates and is contraindicated in neonates with reduced gut motility (post-operatively or drug-induced).

Adverse reactions: Appetite decreased, bezoar, constipation (discontinue—avoid magnesium-containing laxatives), diarrhea, electrolyte imbalance, epigastric discomfort, GI disorders, increased risk of infection, nausea, necrosis (in combination with sorbitol), vomiting

Interaction with other medicines: Has the potential to bind to other orally administered medications decreasing GI absorption and efficacy. Dosing separation from other orally administered medications is recommended.

Concomitant use not recommended, Sorbitol (oral or rectal): Concomitant use of Sorbitol with sodium polystyrene sulfonate is not recommended due to cases of intestinal necrosis and other serious GI adverse reactions, which may be fatal.

To be used with caution, Cation-donating agents: may reduce the potassium binding effectiveness of sodium polystyrene sulphonate. Non-absorbable cation-donating antacids and laxatives: There have been reports of systemic alkalosis following concurrent administration of cation-exchange resins and non-absorbable cation-donating antacids and laxatives such as magnesium hydroxide and aluminium carbonate. Aluminium hydroxide: Intestinal obstruction due to concretions of aluminium hydroxide has been reported when aluminium hydroxide has been combined with the resin. Digitalis-like drugs: The toxic effects of digitalis on the heart, especially various ventricular arrhythmias and A-V nodal dissociation, are likely to be exaggerated if hypokalaemia is allowed to develop. Lithium: Possible decrease of lithium absorption. Levothyroxine: Possible decrease of levothyroxine absorption.

Sodium Hydrogen Carbonate (Sodium Bicarbonate)

ATC code: B05CB04

Tablet (scored), 600 mg, 1 g, LOU 5

Indications and dose

Adult

Alkalinisation of urine, Relief of discomfort in mild urinary-tract infections, Oral: 3 g every 2 hours until urinary pH exceeds 7, to be dissolved in water

Maintenance of alkaline urine, Oral: 5–10 g daily, to be dissolved in water

Chronic acidotic states such as uraemic acidosis or renal tubular acidosis, Oral: 4.8 g daily, (57 mmol each of Na+ and HCO3-), higher doses may be required and should be adjusted according to response

Paediatric

Alkalinisation of urine, Relief of discomfort in mild urinary-tract infections, Maintenance of alkaline urine, Chronic acidotic states such as uraemic acidosis or renal tubular acidosis, Oral:

Neonate: Initially 1–2 mmol/kg daily in divided doses, adjusted according to response.

Child: Initially 1–2 mmol/kg daily in divided doses, adjusted according to response

Contraindications: Salt restricted diet

Precautions: Avoid prolonged use in urinary conditions, cardiac disease, Elderly patients on sodium-restricted diet, respiratory acidosis

Adverse effects: Abdominal cramps, burping, flatulence, hypokalaemia, metabolic alkalosis

Interaction with other medicines: Acalabrutinib, Amphetamine, Benzphetamine, Cabotegravir, Dextroamphetamine, Digoxin, Erdafitinib, Gefitinib, Ketoconazole, Ledipasvir, Lisdexamfetamine, Mefenamic Acid, Memantine, Methamphetamine, Neratinib, Octreotide, Pazopanib, Rilpivirine, Selpercatinib, Chloroquine.

Tolvaptan

ATC code: C03XA01

Tablet, 15 mg, LOU 5

Indications and dose

Adult

Hyponatraemia secondary to (SIADH) (initiated in hospital or under specialist supervision, Oral: Initially 15 mg once daily, increased if necessary up to 60 mg once daily, a reduced starting dose of 7.5 mg once daily should

be considered for patients at risk of overly rapid correction of serum-sodium concentration.

Paediatric

No or insufficient experience in children and adolescents therefore its use is not recommended.

Contraindications: Hypersensitivity to the active substance or to any of the excipients or to benzazepine or benzazepine derivatives

Elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of tolvaptan

Anuria, Volume depletion, Hypernatraemia, Patients who cannot perceive or respond to thirst, Pregnancy, Breastfeeding

Precautions: Abnormal liver function tests and/or signs or symptoms of liver injury (do not initiate if the criteria for permanent discontinuation are met), diabetes mellitus. Patients at risk of outflow obstruction (increased risk of acute retention)

When used for autosomal dominant polycystic kidney disease serum-sodium abnormalities (correct before treatment initiation)

When used for hyponatraemia secondary to SIADH patients at risk of demyelination syndromes (e.g. hypoxia, alcoholism and malnutrition)

Adverse effects: Common or very common: Appetite decreased, asthenia, constipation, dehydration, diarrhoea, dizziness, dry mouth, dyspnoea, GI discomfort, GERD, headache, hepatic disorders, hyperglycaemia, hypernatraemia, hyperuricaemia, insomnia, muscle spasms, palpitations, polydipsia, skin reactions, thirst, urinary disorders, weight decreased

Acute hepatic failure (cases requiring liver transplantation reported). Interrupt treatment and perform liver-function tests promptly if symptoms of hepatic impairment occur (anorexia, nausea, vomiting, fatigue, abdominal pain, jaundice, dark urine, pruritus)

Interactions with other medicines:

Concomitant use of medicinal products that are moderate CYP3A inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) or strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, ritonavir, and clarithromycin) increase tolvaptan exposure.

Concomitant use of medicinal products that are potent CYP3A inducers (e.g., rifampicin) will decrease tolvaptan exposure and efficacy. Co-administration of tolvaptan with rifampicin reduces Cmax and AUC for tolvaptan by about 85%. Therefore, concomitant administration of tolvaptan with potent CYP3A inducers (e.g., rifampicin, rifabutin, rifapentin, phenytoin, carbamazepine, and St. John's Wort) is to be avoided.

Concomitant use of tolvaptan with medicinal products that increase serum sodium concentration may result in a higher risk for developing hypernatraemia and is therefore not recommended.

While there does not appear to be a synergistic or additive effect of concomitant use of tolvaptan with loop and thiazide diuretics, each class of agent has the potential to lead to severe dehydration, which constitutes a risk factor for renal dysfunction. If dehydration or renal dysfunction becomes evident, appropriate action must be taken which may include the need to interrupt or reduce doses of tolvaptan and/or diuretics and increased fluid intake. Other potential causes of renal dysfunction or dehydration must be evaluated and addressed.

Tolvaptan increased plasma levels of lovastatin by 1.3- to 1.5-fold. Even though this increase has no clinical relevance, it indicates tolvaptan can potentially increase exposure to CYP3A4 substrates.

Patients receiving digoxin or other narrow therapeutic P-gp substrates (e.g., dabigatran) must therefore be managed cautiously and evaluated for excessive effects when treated with tolvaptan.

It is not recommended to administer Tolvaptan with vasopressin analogues.

31.2. Parenteral

Calcium Gluconate

ATC code: A12AA03

Injection, 100 mg/mL (10%), 10-mL amp, LOU 4

Indications and dose

Adult

Severe acute hypocalcaemia or hypocalcaemic tetany, initially by slow IV injection: Initially 10–20 mL, calcium gluconate injection 10% (providing approximately 2.25–4.5 mmol of calcium) should be administered with plasma-calcium and ECG monitoring, and either repeated as required or, if only temporary improvement, followed by a continuous IV infusion to prevent recurrence, alternatively, *by continuous IV infusion*, initially 50 mL/hour, adjusted according to response, infusion to be administered using 100 mL of calcium gluconate 10% diluted in 1 L of glucose 5% or sodium chloride 0.9%

Acute severe hyperkalaemia (plasma-potassium concentration above 6.5 mmol/L or in the presence of ECG changes), by slow IV injection: 10–20 mL, calcium gluconate 10% should be administered, dose titrated and adjusted to ECG improvement

Calcium deficiency, Mild asymptomatic hypocalcaemia: oral: Dose according to requirements

Paediatric

Severe acute hypocalcaemia or hypocalcaemic tetany, Acute severe hyperkalaemia By slow IV injection:

Neonate: 0.11 mmol/kg for 1 dose, to be given over 5–10 minutes, some units use a dose of 0.46 mmol/kg (2 mL/kg calcium gluconate 10%) for hypocalcaemia.

Child: 0.11 mmol/kg, to be given over 5–10 minutes, maximum 4.5 mmol (20 mL calcium gluconate 10%)

Contraindications:

Hypersensitivity to the active substance or to any of the excipients

Patients with severe renal failure, Patients with hypercalcaemia (e.g., in hyperparathyroidism, hypervitaminosis D, neoplastic disease with decalcification of bone, renal insufficiency, immobilization osteoporosis, sarcoidosis, milk-alkali syndrome),

Patients with hypercalciuria, Patients receiving cardiac glycosides.

Co-administration with ceftriaxone in: Premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life) and Full-term newborns (up to 28 days of age) because of the risk of precipitation of ceftriaxone-calcium

Repeated or prolonged treatment, including as an IV infusion, in children (less than 18 years of age) and those with impaired renal function, due to the risk of exposure to aluminium.

Precautions:

Solutions containing calcium should be administered slowly to minimize peripheral vasodilation and cardiac depression.

IV injections should be accompanied by heart rate or ECG control because bradycardia with vasodilatation or arrhythmia can occur when calcium is administered too quickly.

Plasma levels and urinary excretion of calcium should be monitored when high-dose parenteral calcium is administered.

Calcium salts are irritant. The infusion site must be monitored regularly to ensure extravasation injury has not occurred.

Patients receiving calcium salts should be monitored carefully to ensure maintenance of correct calcium balance without tissue deposition.

High vitamin D intake should be avoided.

Adverse effects:

Cardiovascular and other systemic undesirable effects are likely to occur as symptoms of acute hypercalcaemia resulting from IV overdose or too rapid IV injection. Their occurrence and frequency is directly related to the administration rate and the administered dose.

Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full-term newborns (aged <28 days) who had been treated with IV ceftriaxone and calcium.

Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in newborns is due to their low blood volume and the longer half-life of ceftriaxone compared with adults.

Adverse effects only occurring with improper administration technique:

Reddening of skin, burning sensation or pain during IV injection may indicate accidental perivascular injection, which may lead to tissue necrosis.

Interactions with other medicines:

The effects of digoxin and other cardiac glycosides may be potentiated by calcium, which may result in serious toxicity. Therefore, IV administration of calcium preparations to patients under therapy with cardiac glycosides is contraindicated.

Co-administration of calcium and epinephrine attenuate epinephrine's β-adrenergic effects in postoperative heart surgery patients.

Calcium and magnesium mutually antagonise their effects.

Calcium may antagonise the effect of calcium antagonists (CCBs).

Combination with thiazide diuretics may induce hypercalcaemia as these medicinal products reduce renal calcium excretion.

Physical incompatibilities including interaction with ceftriaxone

Glucose Injectable Solution

ATC code: V06DC01

5% (isotonic) (500-mL infusion pack), LOU 2

10% (hypertonic) (500-mL infusion pack), LOU 2

50% (hypertonic) (50-mL amp), LOU 4

Indications and dose

Adult

Fluid replacement without significant electrolyte deficit, treatment of Hypoglycaemia, By IV infusion: determined on the basis of clinical and, whenever possible, electrolyte monitoring.

Treatment of hypoglycaemia, By IV infusion: 50% glucose solution into

a large vein, 25 mL.

Paediatric

Fluid replacement, IV infusion:

Neonate, Infant or **Child:** determined on the basis of clinical and, whenever possible, electrolyte monitoring.

Neonatal hypoglycaemia, IV:

Neonate: initial dose of 2.5 mL/kg of glucose 10% over 5 minutes, then 5 mL/kg/hour of glucose 10%. Recheck glucose after initial dose.

Hypoglycaemia, IV: (doses should be given into a large vein because of risk of superficial thrombophlebitis and through a large gauge needle)

Infant or **Child:** 5 mL/kg of glucose 10% as a bolus.

Contraindications: The solution is contraindicated in patients presenting with: Uncompensated diabetes and diabetes insipidus, Hyperosmolar coma, Haemodilution and extracellular hyperhydration or hypervolaemia, Hyperglycaemia and hyperlactataemia, Severe renal insufficiency (with oliguria/anuria), Uncompensated cardiac failure, General oedema (including pulmonary and brain oedema) and ascitic cirrhosis, Other known glucose intolerances (such as metabolic stress situations).

Hypersensitivity to the active substance.

Precautions: Glucose IV infusions are usually isotonic solutions. In the body, however, glucose containing fluids can become extremely physiologically hypotonic

due to rapid glucose metabolization

Patients with non-osmotic vasopressin release (e.g., in acute illness, pain, post-operative stress, infections, burns, and CNS diseases), patients with heart-, liver- and kidney diseases and patients exposed to vasopressin agonists are at particular risk of acute hyponatraemia upon infusion of hypotonic fluids.

Children, women in the fertile age and patients with reduced cerebral compliance (e.g., meningitis, intracranial bleeding, and cerebral contusion) are at particular risk of the severe and life-threatening brain swelling caused by acute hyponatraemia.

Adverse effects: Glucose injections, especially if hypertonic, have a low pH and may cause venous irritation and thrombophlebitis, fluid and electrolyte. Disturbances, oedema or water intoxication (on prolonged administration or rapid infusion of large volumes of isotonic solutions), hyperglycaemia (on prolonged administration of hypertonic solutions).

Interactions with other medicines: Both the glycaemic effects of glucose solution and its effects on water and electrolyte balance should be considered when using glucose solution in patients treated with other substances that affect glycaemic control, or fluid and/or electrolyte balance.

Concomitant administration of catecholamines and steroids decreases the glucose up-take.

Glucose + Sodium Chloride

ATC code: B05BB02

Injectable solution glucose 5% + sodium chloride 0.9%, LOU 2

Indications and dose

Adult

Fluid replacement, By IV infusion: determined on the basis of clinical and, whenever possible, electrolyte monitoring

Paediatric

Fluid replacement, IV infusion:

Neonate, Infant or Child: determined on the basis of clinical and, whenever possible, electrolyte monitoring.

Precautions: Hyponatraemia, hypernatraemia, restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary oedema, meningitis, head injury.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Restrict intake dependent on renal function and fluid requirements or restrictions.

Adverse effects: Dilutional hyponatraemia especially in children when using 0.45% sodium chloride (rapid decrease in serum sodium may result in cerebral oedema), administration of large doses may give rise to oedema.

Interactions with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

- Indicated when there is combined sodium and water depletion. It is preferable to use 5% glucose with 0.9% sodium chloride to avoid rapid changes in sodium.

Potassium Acid Phosphate Solution

ATC code: B05XA06

Sterile Aqueous Solution – Injection (potassium acid phosphate 13.6%w/v), LOU 4

Indications and dose

Adult

Electrolyte replacement therapy for potassium and phosphate ions, by slow IV infusion: The equivalent of 10mmol (310mg) of phosphorus a day. Diluted before use.

Paediatric

Electrolyte replacement therapy for potassium and phosphate ions, by slow IV infusion: The equivalent of 1.5-2.0 mmol (46.5 to 62mg) of phosphorus a day. Diluted before use.

Contraindications: Hyperphosphataemia. *Risk - Benefit should be considered when the following medical problems exist*:

- Conditions in which high phosphate concentrations may be encountered, such as hypoparathyroidism, chronic renal disease.
- Conditions in which low calcium concentrations may be encountered, such as: hypoparathyroidism, osteomalacia, acute pancreatitis, chronic renal disease, rickets.
- Sensitivity to Potassium or Phosphates.
- Cardiac disease, particularly in digitalized patients.
- Conditions in which high potassium concentrations may be encountered, such as: Severe adrenal insufficiency - Addison's disease, acute dehydration, severe renal insufficiency, extensive tissue breakdown, such as severe burns.
- Myotonia congenita

Renal impairment: Contraindicated in severe renal function impairment - less than 30% of normal, urolithiasis.

Precautions: The product must be diluted before use. Electrocardiogram (may be required at regular intervals during intravenous therapy)

Pregnancy: There has been no adequate and well controlled studies carried out in this area in either humans or animals.

Breastfeeding: It is not known if phosphates are excreted in breast milk. However, problems in nursing infants have not been documented

Adverse effects: Fluid retention, hyperkalemia, hypernatremia, hyperphosphatemia, hypercalcemic tetany.

Interactions with other medicines (*indicates serious): Captopril, Potassium - Sparing Diuretics, Enalapril, Lisinopril, Adrenocorticoids, Glucocorticoids, Mineralocorticoids, Corticotropin (ACTH), Anabolic Steroids or Androgens. Potassium containing medications (concurrent use with potassium phosphate may result in hyperkalaemia). *Digitalis Glycosides: Use in digitalized patients with severe or complete heart block is not recommended because of possible hyperkalaemia. Concurrent use with phosphate may cause or worsen renal damage. Salicylates: Concurrent use with potassium and sodium phosphates combination or monobasic potassium phosphate may increase plasma concentrations of salicylates since salicylate excretion is decreased in acidified urine; addition of these phosphates to patients stabilized on a salicylate may lead to toxic salicylate concentrations.

Potassium Chloride

ATC code: B05XA01

Injectable solution for dilution 15% (10-mL amp), LOU 4

Indications and dose

Adult

Electrolyte imbalance, by slow IV infusion: depending on the deficit or the daily maintenance requirements

Paediatric

Maintenance IV:

Neonate, Infant or Child: 1–2 mmol/kg/day.

Acute deficiency, IV:

Neonate, Infant or Child: 0.2–0.4 mmol/kg/hour for 4–6 hours via a central line in an ICU setting with ECG monitoring only. Monitor serum potassium after 3 hours and adjust dose accordingly. Dilute to 120 mmol/L or weaker.

Contraindications: Plasma potassium concentration above 5 mmol/L.

Precautions: Specialist advice and ECG monitoring, renal impairment, cardiac disease, patients receiving potassium-sparing drugs.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Moderate to severe: avoid routine use, high risk of hyperkalaemia.

Adverse effects: With rapid IV administration Hyperkalaemia, arrhythmias and cardiac arrest, heart block, hypotension.

Common: Hyperkalaemia, nausea, vomiting, pain at site of injection, phlebitis.

Rare: Mental confusion, diarrhoea, abdominal pain, GI lesions, flatulence, muscle weakness, paraesthesia, flaccid paralysis.

Symptoms of hyperkalaemia Paraesthesia of extremities, listlessness, confusion, weakness, flaccid paralysis, hypotension, cardiac arrhythmias, cardiac arrest, heart block. ECG changes: peaking of T waves, shortening of P wave, shortening of ST segment and prolongation of QT interval.

Interactions with other medicines (*indicates serious):

* Ciclosporin: increased risk of hyperkalaemia.

* Enalapril: increased risk of severe hyperkalaemia.

* Spironolactone: risk of hyperkalaemia.

Notes:

- Consider special storage requirements for IV potassium salts given that administration errors may lead to fatal outcomes.
- Administration Peripheral and central line: dilute to 40 mmol/L or weaker (preferably use a pre-mixed solution) and infuse at a maximum rate of 0.2 mmol/kg/hour.
- If central line access is available and in an ICU setting with ECG monitoring only: dilute to 120 mmol/L or weaker and infuse at a maximum rate of 0.4 mmol/kg/hour.
- Monitoring during administration hourly: check IV site for signs of extravasation and document volume infused.
- Monitor serum potassium and pulse, respiratory rate, blood pressure, urine output and other electrolytes every 4–6 hours until stable, then daily, repeat sample if haemolysed as this can result in a falsely elevated potassium result.
- If potassium level is high: ensure blood sample was not haemolysed, was actually a venous sample and was not taken from the line where potassium was being infused. Repeat potassium measurement every 30–60 minutes.
- Hyperkalaemia may require treatment with calcium gluconate, insulin and glucose, salbutamol, calcium resonium, furosemide and sodium bicarbonate or other measures.
- Extreme caution is necessary when giving potassium chloride infusions as an overdose can cause fatal cardiac arrest.
- Never give a bolus of fluids containing potassium chloride.
- Never flush after potassium chloride infusions.
- Ready-mixed infusion solutions containing potassium should be used when available.
- If potassium chloride concentrate is used for preparing an infusion, the infusion solution should be thoroughly mixed by inverting the fluid bag at least ten times.
- Do not add potassium to a bag that is already hanging.
- Local policies on avoiding inadvertent use of potassium chloride concentrate should be followed.

Sodium Chloride

ATC code: B05XA03

Injectable solution (infusion) 0.45% (hypotonic), 500 mL, [in collapsible bottle or Euro cap], LOU 4

Injectable solution 0.9% (isotonic), 100 mL, 250 mL, 500 mL, [in collapsible bottle or Euro cap], LOU 2

Injectable solution 30% (hypertonic), 10 mL amp, LOU 5

Injectable solution 3% (hypertonic), 100 mL , LOU 5

Indications and dose

Adult

Electrolyte and fluid replacement, *By IV infusion*: determined on the basis of clinical and, whenever possible, electrolyte monitoring

Paediatric

Electrolyte and fluid replacement, *IV infusion:*

Neonate, Infant or Child: determined on the basis of clinical and, whenever possible, electrolyte monitoring.

Precautions: Restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary oedema, toxaemia of pregnancy, cardiorespiratory disease, hepatic cirrhosis and in children receiving glucocorticoids.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Administration of large doses may give rise to sodium accumulation and oedema.

Interactions with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

» Also known as normal saline, this term should not be used to describe sodium chloride IV infusion 0.9%, as error may occur.

Sodium Hydrogen Carbonate (Sodium Bicarbonate)

ATC code: B05XA02

Injectable solution 8.4% (10-mL amp), LOU 2

Indications and dose

Adult

Severe metabolic acidosis IV (by continuous infusion with 1.4% solution co-infused with isotonic sodium chloride, or by slow infusion of 8.4% solution)

Paediatric

Severe metabolic acidosis IV (by continuous infusion with 1.4% solution co-infused with isotonic sodium chloride, or by slow infusion of 8.4% solution)

Neonate, infant, or **child:** mmol of HCO_3 = 0.5 × weight (kg) × (24 – serum mmol of HCO_3/L); half the required volume of sodium hydrogen carbonate solution should be infused and the patient's clinical progress and serum HCO_3 should be monitored before giving the remaining half.

1.4% solution contains, per 1 mL, 0.167 mmol of Na and 0.167 mmol of HCO_3.

8.4% solution contains, per 1 mL, 1 mmol of Na and 1 mmol of HCO_3.

If acid–base status not available, IV infusion

Child over 2 years: 1–5 mmol/kg; subsequent doses should be based on patient's acid–base status; extreme care should be taken when administering to patients without confirmed metabolic acidosis.

Contraindications: Metabolic or respiratory alkalosis, hypocalcaemia, hypochlorhydria, hypernatraemia, unknown abdominal pain, inadequate ventilation during cardiopulmonary resuscitation, excessive chloride losses. Not for intra-arterial or intra-osseous injection.

Precautions: Restrict intake in impaired renal function, congestive heart failure, hypertension, peripheral and pulmonary oedema, other sodium-retaining conditions.

Caution should be taken when administering to patients under 2 years as hypernatraemia due to rapid injection may occur.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Severe: avoid, specialized role in some forms of renal disease.

Adverse effects: Excessive administration may cause hypokalaemia and metabolic alkalosis, especially in renal impairment, large doses may give rise to sodium accumulation and oedema.

Extravasation may lead to tissue necrosis or ulceration.

Interaction with other medicines (*indicates serious):

Epinephrine: physically incompatible, do not infuse together with sodium hydrogen carbonate.

* Flecainide: can decrease renal excretion of flecainide and lead to flecainide toxicity.

Quinine: sodium hydrogen carbonate may increase the levels/effect of quinine.

Notes

» Monitor for hypokalaemia and hyperkalaemia. Na+ content = 1 mmol/mL (8.4%) and HCO_3

» Also known as sodium bicarbonate, sodium acid carbonate and $NaHCO_3$. Avoid extravasation, may cause cellulitis and tissue necrosis due to the hypertonicity of sodium hydrogen carbonate. Preferably administer into a large vein.

» –1 mmol/mL (8.4%). 0.18 mmol/mL ≈ 1.5% ≈ isotonic.

» Rapid injection (10 mL/min) of sodium hydrogen carbonate solutions in children up to 2 years of age may produce hypernatraemia, decreased cerebrospinal fluid pressure and possible intracranial haemorrhage.

» Avoid extravasation, tissue necrosis can occur due to the hypertonicity of sodium hydrogen carbonate.

Sodium Lactate Compound (Hartmanns/ Ringers Lactate)

ATC code: B05BB01

Injectable solution (infusion), BP formula (500 mL),

LOU 2

Indications and dose

Adult

Preoperative and perioperative fluid and electrolyte replacement, hypovolaemic shock.

Metabolic acidosis, by slow IV injection of a strong solution (up to 8.4%) or by continuous IV infusion of a

weaker solution (usually 1.4%): an amount appropriate to the body base deficit

Paediatric

Fluid and electrolyte replacement or hypovolaemic shock, IV infusion:

Neonate, Infant or Child: determined on the basis of clinical and, whenever possible, electrolyte monitoring.

Contraindications: Hypercalcaemia or hypochlorhydria, hypernatraemia, lactic acidosis, severe acidosis requiring immediate repletion of plasma bicarbonate, concomitant treatment with ceftriaxone (ceftriaxone should not be used in neonates less than 28 days of age if they are receiving (or are expected to receive) calcium-containing IV products. In patients > 28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid).

Precautions: Restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary oedema, concurrent corticosteroids, conditions impairing lactate utilization, metabolic or respiratory alkalosis.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse effects: Excessive administration may cause metabolic alkalosis, excessive administration may cause hyperkalaemia, administration of large doses may give rise to oedema.

Interaction with other medicines (*indicates serious)

* Ceftriaxone

Water For Injection

ATC code: V07AB

Injection, 10-mL amp, LOU 2

Idications and dose

Adult and Paediatric

In preparations intended for parenteral administration and in other sterile preparations.

For dissolving or diluting agents for parenteral administration.

The dosage for water for injections is that required to dissolve or dilute other agents. Aseptic technique should be followed when preparing solutions for parenteral administration. Check the product information of any substance, preparation or drug before use to ensure appropriate solubility, dilution or compatibility with other additives.

Precautions: Should not be administered in large quantities as excessive water can lead to water intoxication with disturbances of the electrolyte balance.

Hepatic impairment: Dose reduction not necessary.

Renal impairment: Dose reduction not necessary.

Adverse reactions: No Adverse reactions documented except in overdose (see Notes).

Interaction with other medicines: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes:

» Care should be exercised that solutions prepared with water for injection are isotonic before use. If large volumes of water for injection are inadvertently injected without first ensuring isotonicity, the hypotonic effects may include local cell damage or haemolysis. Electrolyte abnormalities are possible.

32. Vitamins & Minerals

Ascorbic Acid (Vitamin C)

ATC code: A11GA01

Tablet, 50 mg, 250 mg, 1 g, LOU 2

Indications and dose

Adult

Treatment of scurvy, Oral

1 to 2 g for the first 2 days then 500 mg daily for a week

Alternative dose: 250mg four times daily for a week

Prophylaxis of scurvy, Oral

Recommended daily intake

Males: 90mg/day

Females: 75mg/day

Pregnancy: 85mg/day; not to exceed 2000mg/day (80mg if less than 18years old; not to exceed 1800mg/day)

Paediatric

Treatment of scurvy, Oral

Not less than 250 mg daily in 1–2 divided doses until clinical signs of scurvy disappear.

Prophylaxis of scurvy, Oral

25–75 mg daily.

Recommended daily intake

Infant 0–6 months: 25 mg/day

Child 7–12 months: 30 mg/day.

Child 1–8 years:35 mg/day,

Child over 9 years: 40 mg/day.

Contraindications

Hyperoxaluria.

Hepatic impairment: dose reduction not necessary.

Renal impairment: dose reduction not necessary.

Adverse effects: Adverse effects only occur in very large doses.

Rare: nausea, diarrhoea, headache, fatigue, hyperoxaluria.

Interaction with other medicines:

Aluminium hydroxide: ascorbic acid may increase the level/effect.

Deferoxamine: ascorbic acid may increase the level/effect.

Notes:

- Ascorbic acid also has antioxidant effects.
- Tablets may be crushed and mixed with a small amount of food or water and given immediately. Ascorbic acid is quickly oxidized when in solution.

Calcitriol (Vitamin D3) (Vitamin D3)

ATC code: A11CC04

Capsule, 250 micrograms, LOU 4

Injection, 1 microgram/mL (1 mL), LOU 4

Indications and dose

Adult

Hypocalcaemia - hypoparathyroidism, postsurgical or idiopathic, Oral

Initial, 0.25 micrograms/day in the morning, dose may be increased at 2- to 4-wk intervals, usual dose range, 0.5 to 2 micrograms once daily.

Hypocalcaemia – pseudohypoparathyroidism, Oral

Initial, 0.25 micrograms/day in morning, dose may be increased at 2- to 4-wk intervals, usual dose range, 0.5 to 2 micrograms once daily.

Hypocalcaemia – renal dialysis (chronic), Oral

Initial, 0.25 micrograms daily or every other day (may require 0.5 to 1 micrograms/day), increases of 0.25 micrograms/day may be made at 4 to 8 wk. intervals.

Hypocalcaemia – renal dialysis (chronic), IV

1 to 2 micrograms/day 3 times/wk. on approximately every other day (may require 0.5 to 4 micrograms/day 3 times/wk.), may increase by 0.5 to 1 micrograms/dose at 2 to 4 wk. intervals to optimal response.

Paediatric

Hypocalcaemia - hypoparathyroidism, postsurgical or idiopathic, Oral

Child 1 to 5 years: 0.25 micrograms/day orally in the morning, dose may be increased at 2- to 4-wk intervals, usual dose range, 0.25 to 0.75 micrograms orally once daily.

6 years of age and older: initial, 0.25 micrograms/day orally in morning, dose may be increased at 2- to 4-wk intervals, usual dose range, 0.5 to 2 micrograms orally once daily.

Contraindications

Hypercalcemia, pre-existing

Hypersensitivity to calcitriol, any component of the product, or drugs of the same class

Vitamin D toxicity, pre-existing

Precautions

Excessive dosage may result in hypercalcemia, hypercalciuria, and hyperphosphatemia, monitoring recommended

Hypercalcemia has been reported, increased risk with concomitant use of agents known to increase the serum calcium level and in patients receiving calcium supplements or high doses of vitamin D. Monitoring recommended and therapy interruption may be needed until normalized.

Chronic hypercalcemia may occur with vitamin D overdosage which may lead to generalized vascular

and soft-tissue calcification and nephrocalcinosis, monitoring recommended

Dehydration may increase serum creatinine and risk of hypercalcemia

Inorganic phosphate levels in serum may increase

Patients on dialysis are at increased risk of hypermagnesemia and hyperphosphatemia, avoid magnesium-containing products (e.g., antacids) and high-phosphate diets

Ectopic calcification may occur due to elevated inorganic phosphate levels in patients with pre-existing renal failure

Immobilized patients (e.g., recent surgery) have an increased risk of hypercalcemia

Pregnancy: Foetal risk cannot be ruled out.

Breastfeeding: Use is not recommended and a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother. Whether it is excreted into human milk is unknown, it is presumed that this drug passes into breast milk and If used during breastfeeding, monitor the serum calcium levels of the mother and the infant.

Adverse effects: Common: Endocrine metabolic: hypercalcemia (24%)

Serious: Endocrine metabolic: poisoning by vitamin D, hypercalcemia syndrome

Interaction with other medicines:

Magnesium containing antacids

Agents that increase serum calcium levels

Calcium Carbonate

ATC code: A12AA04

Tablet (chewable), 500 mg, 1.25 g, LOU 4

Indications and dose

Adult

Calcium deficiency: prophylaxis, oral:

RDA is the average daily intake from all sources (diet and supplements) necessary to meet the nutrient requirements of nearly all (97% to 98%) healthy individuals, max is the upper intake level that is unlikely to cause adverse health effects.

19 to 50 years, RDA is 1000 mg elemental calcium per day in divided doses of 500 mg or less each: max 2500 mg per day (guideline dosing)

51 to 70 years (men), RDA is 1000 mg elemental calcium per day in divided doses of 500 mg or less each: max 2000 mg per day (guideline dosing)

51 to 70 years (women), RDA is 1200 mg elemental calcium per day in divided doses of 500 mg or less each: max 2000 mg per day (guideline dosing)

Greater than 70 years, RDA is 1200 mg elemental calcium per day in divided doses of 500 mg or less each: max 2000 mg per day (guideline dosing)

Hypocalcaemia, chronic, oral:

1 to 3 g elemental calcium daily in divided doses

Postmenopausal osteoporosis, oral:

Women 51 years or older, 1200 mg elemental calcium per day total intake (diet plus supplements) in combination with 800 to 1000 IU vitamin D (national osteoporosis foundation guideline dosing)

Renal failure-associated hyperphosphatemia, oral:

Stage 3 to 5 CKD, total dose of elemental calcium from all sources (i.e., dietary and calcium-based phosphate binder) not to exceed 2000 mg/day (guideline dosing)

Stage 5 CKD, total dose of elemental calcium from calcium-based phosphate binder not to exceed 1500 mg/day (guideline dosing)

Paediatric

Calcium deficiency, prophylaxis, oral

RDA is the average daily intake from all sources (i.e., diet and supplements) necessary to meet the nutrient requirements of nearly all (97% to 98%) healthy individuals, max is the upper intake level that is unlikely to cause adverse health effects.

Child 0 to 6 months: RDA is 200 mg elemental calcium per day: max 1000 mg per day

Child 6 to 12 months: RDA is 260 mg elemental calcium per day: max 1500 mg per day

Child 1 to 3 years: RDA is 700 mg elemental calcium per day: max 2500 mg per day

Child 4 to 8 years: RDA is 1000 mg elemental calcium per day: max 2500 mg per day

Child 9 to 13 years: RDA is 1300 mg elemental calcium per day: max 3000 mg per day

Child 14 to 18 years: RDA is 1300 mg elemental calcium per day: max 3000 mg per day

Contraindications

Hypercalcemia (e.g., associated with sarcoidosis, hyperparathyroidism, hypervitaminosis-D, certain cancers)

Precautions

Calcium absorption may occur in patients with absorption disorders, calcium citrate formulation recommended.

Achlorhydria or need to take calcium on an empty stomach, decreased calcium absorption may occur, calcium citrate formulation recommended.

Hypercalcemia has been reported, increased risk with calcium intake above upper-level intake recommendations.

Inflammatory bowel disease: decreased calcium absorption may occur, calcium citrate formulation recommended.

Milk-alkali syndrome (hypercalcemia, metabolic acidosis, renal failure) has been reported, increased risk with calcium intake above the upper-level intake recommendations.

Mineral stores deficiencies (iron, magnesium, zinc), calcium supplementation may decrease mineral absorption which may worsen deficiencies, taking calcium supplement between meals and at bedtime is recommended in at-risk patients.

Reduced calcium absorption may occur with calcium carbonate administration without food.

Renal calculi have been reported, increased risk with calcium intake above the upper-level intake recommendations.

Renal insufficiency has been reported, increased risk with calcium intake above the upper-level intake recommendations.

Vitamin D deficiency: decreased calcium absorption has been reported.

Pregnancy category C: foetal risk cannot be ruled out.

Breastfeeding calcium: infant risk cannot be ruled out.

Adverse effects: Common: constipation, flatulence, swollen abdomen

Serious: MI, urolithiasis, milk alkali syndrome

Interaction with other medicines:

Major:

Acalabrutinib, amphetamine, baloxavir marboxil, benzphetamine, bictegravir, cabotegravir, dextroamphetamine, digoxin, dolutegravir, eltrombopag, elvitegravir, eRDAfitinib, gefitinib, ketoconazole, ledipasvir, lisdexamfetamine, mefenamic acid, methamphetamine, neratinib, octreotide, pazopanib, phenytoin, raltegravir, rilpivirine, selpercatinib, sodium polystyrene sulfonate, vismodegib

Moderate:

Amprenavir, cefditoren pivoxil, chloroquine, chlorothiazide, chlortetracycline, ciprofloxacin, delafloxacin, demeclocycline, doxycycline, enoxacin, gemifloxacin, grepafloxacin, levofloxacin, levothyroxine, lomefloxacin, lymecycline, methacycline, minocycline, norfloxacin, omadacycline, oxytetracycline, pefloxacin, potassium phosphate, potassium phosphate, dibasic potassium phosphate, monobasic, propranolol, rolitetracycline, sarecycline, sodium phosphate, sodium phosphate, dibasic

sodium phosphate, monobasic, sparfloxacin, strontium ranelate, tetracycline, ticlopidine, tipranavir, tosufloxacin, zalcitabine.

Calcium Gluconate

ATC code: A12AA03

Injection, 100 mg/mL (10%), 10-mL amp, LOU 4

Indications and dose

Adult

Severe symptomatic hypocalcemia (seizure, laryngospasm, tetany), IV:

1 to 2 grams of calcium gluconate should be administered in 10 minutes and repeated in 10 to 60 minutes until symptoms resolve.

Approximately 100 to 200 mg of elemental calcium should be infused over a period of 10 minutes to treat symptomatic hypocalcemia. Rhythm monitoring with an EKG is recommended during IV calcium bolus (IV push over 10 minutes) administration. 10 to 20 mL of 10% calcium gluconate diluted in 50 to 100 mL dextrose or normal saline intravenously over 10 minutes is recommended. For persistent symptoms, the bolus can be repeated after 10 to 60 minutes until symptoms resolve. After this, follow the steps for moderate to severe hypocalcemia. Patients should not receive bicarbonate or phosphate during calcium administration.

Moderate to severe hypocalcemia (ionized calcium <4 mg/dL) without seizure or tetany, IV: An infusion of approximately 100 mg/hour of elemental calcium can be given to adults over several hours. 4 g calcium gluconate IV over 4 hours, which corresponds to 1 gram of calcium gluconate (1 amp, 10 mL of 10% calcium gluconate) for each hour.

Patients with persistent hypocalcemia can receive a continuous infusion of 5 to 20 mg/kg/hour of calcium gluconate. For example, 1 amp of 10% calcium gluconate in 90 mL of normal saline or 5% dextrose at 100 mL per hour will deliver 10 mg/kg/hour in a 100 kg individual. Ten ampoules of 10% calcium gluconate in 900 mL of normal saline or 5% dextrose will also deliver 10 mg/kg/hour in a 100 kg individual. Based on the patient's weight, intended fluid delivery, and desired IV rate, the clinician can alter the infusion parameters.

Mild hypocalcemia (ionized calcium above 4 to 5 mg/dL), IV: 1 to 2 g calcium gluconate IV over 2 hours. Oral calcium is an option for asymptomatic patients.

Paediatric

Hypocalcaemia (dose depends on clinical condition and serum calcium level), IV:

Neonate:200–800 mg/kg/day as a continuous infusion, or in four divided doses.

Infant or child:200–500 mg/kg/day as a continuous infusion, or in four divided doses.

Treatment of tetany, IV:

Neonate, infant or child:100–200 mg/kg/dose, over 5–10 minutes, may repeat after 6 hours or follow with an infusion with a maximum dose of 500 mg/kg/day.

Contraindications

Conditions associated with hypercalcaemia and hypercalciuria (for example some

Forms of malignant disease), renal calculi, ventricular fibrillation.

Precautions

Sarcoidosis, respiratory failure, acidosis, renal or cardiac disease, avoid extravasation (not to be given SC or IM injection as it will cause tissue necrosis), digitalised patients.

Renal impairment moderate and severe: may require dose adjustment depending upon serum calcium level. Risk of hypercalcaemia and renal calculi.

Hepatic impairment: dose reduction not required.

Adverse effects: bradycardia, arrhythmia, injection site reactions, peripheral vasodilation, fall in blood pressure, tissue necrosis (if extravasation occurs).

Interaction with other medicines with other medicines (*indicates serious)

* ceftriaxone: should not be used in neonates less than 28 days of age if they are receiving (or are expected to

receive) calcium-containing IV products. In patients > 28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid.

* digoxin: large IV doses of calcium salts can precipitate arrhythmias.

Hydrochlorothiazide: increased risk of hypercalcaemia.

Notes:

- Dose information is given as calcium gluconate salt or compounds unless provided otherwise, 10% means there are 10 grams of calcium gluconate in 100 mL of the solvent, water. In 10 mL of 10% calcium gluconate, there is 1 g calcium gluconate salt or compound, which contains 93 mg elemental calcium, which is 4.65 mEq, which is 2.33 mmol. Because calcium has a valence of +2, the milliequivalents are twice the millimoles. 1 mL of 10% calcium gluconate contains 9.3 mg of elemental calcium.
- Monitor serum calcium for duration of treatment.
- For direct IV injection, give over 5–10 minutes (maximum 50–100 mg calcium gluconate per minute).
- For IV infusion: dilute to 50 mg/mL and infuse at 120–240 mg/kg over 1 hour.
- Do not give calcium gluconate by SC or IM injection as extravasation, severe necrosis and sloughing may occur.
- Do not administer with IV ceftriaxone.

Cholecalciferol

ATC code: A11CC05

Oral liquid (drops) 400 IU/mL, LOU 4

Injection (IM/oral) 300,000 IU/1-mL amp, LOU 4

Indications and dose

Adult

Nutritional Supplementation, oral:

RDA: 600 IU (15 micrograms)/day

Pregnant or lactating women: 600 IU (15 micrograms)/day

Osteoporosis, Prophylaxis and treatment, oral:

>50 years: 800–1000 IU (20–25 micrograms) once daily with calcium supplements

Hypoparathyroidism, oral

50,000–200,000 IU (0.625–5 mg) once daily with calcium supplements

Vitamin D-resistant rickets, oral:

12,000–500,000 IU (0.3–12.5 mg) once daily

Familial hypophosphatemia, oral:

10,000–60,000 IU (0.25–1.5 mg) once daily with phosphate supplements

Gastrointestinal, liver or biliary disease associated with malabsorption of Vitamin D, resulting in hypophosphataemia, rickets, and osteomalacia, IM: single dose of 300,000 IU every 3-6 months.

Paediatric

Prevention of vitamin D deficiency, oral:

Neonate: 10 micrograms (400 units) daily.

Infant or child: 10–15 micrograms (400–600 units) daily.

Treatment of vitamin D deficiency, treatment of vitamin D deficiency rickets, oral:

Infant under 6 months:75 micrograms (3000 units) daily, adjusted as necessary.

Infant over 6 months or child: 150 micrograms (6000 units) daily, adjusted as necessary.

Hypocalcaemia associated with hypoparathyroidism, oral:

Child: 1.25–5 mg (50 000–200 000 units) daily with calcium supplements.

Treatment of vitamin D deficiency caused by intestinal malabsorption or chronic liver disease, oral:

Child: 250–625 micrograms (10 000–25 000 units) daily, adjusted as necessary

Recommended daily intake for preventing vitamin D deficiency, oral:

infant 0–12 months: 5 micrograms/day.

Child 1–8 years:5 micrograms/day.

9–14 years: 5 micrograms/day.

Gastrointestinal, liver or biliary disease associated with malabsorption of vitamin D resulting in hypophosphatemia, rickets and osteomalacia, IM:

Child 1-12 years: a bolus dose 300,000IU given in 2 divided doses.

Note: For all age groups dosage should be individualised for each patient dependent upon clinical response and requirements.

Contraindications: Hypercalcaemia, malabsorption syndrome, evidence of vitamin D toxicity, metastatic calcification.

Precautions: Coronary artery disease, renal stones, impaired renal function.

Renal impairment: dose reduction not necessary.

Hepatic impairment: dose reduction not necessary.

Adverse effects: Adverse effects usually only occur in overdose.

anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine.

Interaction with other medicines with other medicines:

There are no known interactions where it is recommended to avoid concomitant use.

Notes

- Also known as vitamin D or vitamin D3.
- Ergocalciferol is vitamin D2 and can be used as an alternative.
- 1000 units = 25 micrograms ergocalciferol = 25 micrograms cholecalciferol.

» Patients receiving pharmacological doses of cholecalciferol should have their plasma calcium concentration checked at regular intervals and whenever nausea or vomiting occur.

» Adequate calcium intake is necessary for a clinical response to vitamin D

Ergocalciferol (Vitamin D2)

ATC code: A11CC01

Oral liquid, 250 micrograms (10,000 IU)/mL, LOU 4

Oral solution, 200 IU/drop, LOU4

Tablet/capsule, 250 micrograms (10,000 IU), 1.25 mg (50,000 IU), LOU 4

Indications and dose

Adult

Familial x-linked hypophosphatemic vitamin D refractory rickets, oral:12,000 to 500,000 IU daily

Hypoparathyroidism, oral: 50,000 to 200,000 IU once daily (plus calcium lactate 4 g 6 times daily)

Vitamin D deficiency, oral: 50,000 IU once weekly for 8 weeks or 6000 IU once daily for 8 weeks to achieve a 25-hydroxycalciferol level greater than 30 nanograms/mL, follow with maintenance dose of 1500 to 2000 IU/day

Obesity, malabsorption syndromes, or concomitant use of medications affecting vitamin D metabolism, oral: 6000 to 10,000 IU once daily for 8 weeks to achieve a 25-hydroxycalciferol level greater than 30 nanograms/mL, follow with maintenance dose of 3000 to 6000 IU/day

*older than 50 years, oral:*50,000 IU once weekly for 8 weeks, may repeat 8-week course if 25-hydroxycalciferol is less than 30 nanograms/mL. Follow with maintenance dose of 50,000 IU once every 2 or 4 weeks

Inadequate sun exposure, oral: 50,000 IU once weekly for 8 weeks, may repeat 8-week course if 25- hydroxycalciferol is less than 30 nanograms/mL. Follow with maintenance dose of 50,000 IU once every 2 or 4 weeks

CKD, stages 2 and 3, oral: 50,000 IU once weekly for 8 weeks, may repeat 8-week course if 25-hydroxycalciferol is less than 30 nanograms/mL. Follow with maintenance dose of 50,000 IU once every 2 or 4 weeks

Granulomatous disorders and some lymphomas, oral: 50,000 IU once weekly for 4 weeks, or every 2 to 4 weeks, follow with maintenance dose of 50,000 IU once monthly. Target 25- hydroxycalciferol level is 20 to 30 nanograms/mL

*Primary or tertiary hyperparathyroidism, oral:*50,000 IU once weekly for 8 weeks, may repeat 8-week course if 25- hydroxycalciferol is less than 30 nanograms/mL. Follow with maintenance dose of 50,000 IU once every 2 or 4 weeks

Nephrotic syndrome, oral: 50,000 IU orally twice weekly for 8 to 12 weeks, may repeat 8- to 12-week course if 25- hydroxycalciferol is less than 30 nanograms/mL. Follow with maintenance dose of 50,000 IU once every 2 or 4 weeks

Pregnant or lactating, oral: 50,000 IU once weekly for 8 weeks, may repeat 8-week course if 25-hydroxycalciferol is less than 30 nanograms/mL. Follow with maintenance dose of 50,000 IU once every 2 or 4 weeks

Paediatric

General dosage information

One IU of vitamin D is equivalent to 25 nanograms cholecalciferol or ergocalciferol.

Familial x-linked hypophosphatemic vitamin D refractory rickets, oral:

Neonatal: initial, 2000 to 4000 IU orally once daily for 6 to 12 weeks, then 200 to 400 IU/day

Child:12,000 to 500,000 IU daily, dosage must be individualized.

Hypoparathyroidism, oral:

Child all ages: 50,000 to 200,000 IU orally once daily (plus calcium lactate 4 g 6 times daily), dosage must be individualized.

Vitamin D deficiency, prophylaxis in children with inadequate intake of vitamin D fortified milk or food, oral:

Child all ages: 400 IU daily

Contraindications: Abnormal sensitivity to the toxic effects of vitamin D, hypercalcemia, hypervitaminosis d, malabsorption syndrome

Precautions

Administration: adequate dietary calcium is necessary for clinical response to vitamin D therapy.

Administration: evaluate vitamin D intake from fortified foods, dietary supplements, and self-administered and prescription drug sources.

Endocrine and metabolic: the range between therapeutic and toxic doses is narrow in patients with vitamin D-resistant rickets, monitoring recommended.

Endocrine and metabolic: hyperphosphatemia may occur. Prevent metastatic calcification by maintaining normal serum phosphorus levels via administration of aluminium gels as intestinal phosphate binders and/or dietary phosphate restriction, monitoring recommended.

Endocrine and metabolic: when treating hypoparathyroidism, dihydrotachysterol, IV calcium, and/or parathyroid hormone may be required during treatment.

Immunologic: hypersensitivity to vitamin D, particularly in infants with idiopathic hypercalcemia

Immunologic: tartrazine sensitivity, increased risk of allergic reactions including bronchial asthma in susceptible patients, especially in patients with concomitant aspirin sensitivity

Pregnancy category: foetal risk cannot be ruled out.

Breastfeeding, maternal medication usually compatible with breastfeeding. Who: compatible with breastfeeding.

Infant risk is minimal.

Adverse effects: Common: constipation, loss of appetite, nausea

Serious: hypercalcemia, hypervitaminosis renal: renal impairment

Niacinamide

ATC code: A11HA01

Tablet, 500 mg, LOU 3

Indications and dose

Adult

Pellagra, Oral: 300–500 mg/day, divided into 2–3 doses.

Paediatric

Pellagra, Oral:

Child all ages: 100–300 mg/day, divided into 2–3 doses

Contraindications: Active peptic ulcer disease, hypersensitivity to niacinamide products, liver disease

Precautions

Diabetes, gallbladder disease, gout, history of liver disease, history of peptic ulcer, pregnancy/breastfeeding

Pregnancy: Foetal risk is minimal.

Breastfeeding: Infant risk cannot be ruled out.

Adverse effects: Common: neurologic: dizziness

Serious, hepatic: hepatotoxicity (rare)

Interaction with other medicines: Moderate - Carbamazepine (probable)

Omega 3 Fatty Acids

ATC code: C10AX06

Tablet/capsule, 1 g, LOU 2

Liquid, 250 mg to 500 mg/100 mL, (100 to 200 mL), LOU 2

Indications and dose

Adult

*Hypertriglyceridemia, adjunct to diet in adults with triglyceride levels 500 mg/dL or higher, Omega – 3 deficiency in cardiovascular patients, oral:*4g once daily or 2g twice daily

Paediatric

Child below 18 years: Safety and efficacy not established in paediatric patients

Contraindications

Hypersensitivity (e.g., anaphylactic reaction) to omega-3-acid esters or any product component

Precautions

Cardiovascular: symptomatic atrial fibrillation or flutter may recur more often with treatment in patients with paroxysmal or persistent atrial fibrillation, especially during the first 2 to 3 months of therapy

Endocrine: LDL cholesterol increases have been reported, monitoring recommended

Hepatic: ALT or AST elevations may occur,

monitoring recommended in patients with hepatic impairment

Immunologic: use caution in patients with known hypersensitivity to fish or shellfish

Pregnancy category C: foetal risk cannot be ruled out.

Breastfeeding milk effects are possible.

Adverse effects: Common: GI: burping, indigestion, taste sense altered

Serious: Immunologic: anaphylaxis

Note:

» Evaluate triglyceride levels carefully prior to initiating treatment.

Pyridoxine (Vitamin B_6)

ATC code: A11HA02

Tablet, 25 mg (as HCl), LOU 2

Tablet (scored), 50 mg (as HCl), LOU 2

Indications and dose

Adult

*Pyridoxine Deficiency, oral:*2.5–10 mg/day PO

Nausea in Pregnancy, oral: 10–25 mg every 8 hours

Prevention of Peripheral Neuropathy, Patients treated with isoniazid for Mycobacterium TB, oral: 25–50 mg/day

Paediatric

Metabolic disorders responsive to pyridoxine, sideroblastic anaemia, oral:

Neonate: 50–100 mg 1–2 times daily.

Infant or child: 50–250 mg 1–2 times daily.

Treatment of isoniazid-induced neuropathy, Oral:

Neonate: 5–10 mg daily.

Infant or child: 10–20 mg 2–3 times daily.

Prevention of isoniazid-induced neuropathy, Oral:

Neonate: 5 mg daily.

Infant or child: 5–10 mg daily.

Adverse effects: Generally well tolerated, but chronic administration of high doses may cause Peripheral neuropathies and headache.

Interaction with other medicines with other medicines: There are no known interactions where it is recommended to avoid concomitant use.

Retinol(Vitamin A)

ATC code: A11CA01

Capsule, 50,000 IU (as palmitate), LOU 2

100,000 IU (as palmitate), LOU 2

200,000 IU (as palmitate), LOU 2

Indications and dose

Adult

Vitamin A deficiency, oral:

Prophylaxis: 50000 IU once per day

Xeropthalmia, oral:

Recommended dose except for females of reproductive age: 200,000 units orally once daily for 2 days. Repeat dose again after 2 weeks

Females of reproductive age with night blindness or

Bitot's spots: 5,000-10,000 units per day; 10,000 units per day maximum of 25,000 units once weekly for no more than 4 weeks

Paediatric

Prevention of vitamin A deficiency (universal or targeted distribution programmes), oral:

Infant under 6 months: 50 000 IU single dose.

Infant 6–12 months: 100 000 IU every 4–6 months.

Child over 12 months: 200 000 units every 4–6 months.

A dose should preferably be administered with measles vaccination.

Treatment of xerophthalmia caused by vitamin A deficiency, oral:

Infant under 6 months: 50 000IU on diagnosis, repeated the next day and then after 2 weeks.

Infant 6–12 months: 100 000 IU immediately on diagnosis, repeated next day and then after 2 weeks.

Child over 12 months: 200 000 IU on diagnosis, repeated next day and then after 2 weeks.

Measles (unless the child has already had adequate treatment with retinol for measles), oral:

Infant under 6 months: 50 000IU daily for 2 days.

Infant 6–11 months: 100 000 IU daily for 2 days.

Infant or child 11 months–5 years:200 000 IU daily for 2 days.

If the child shows any eye signs of vitamin A deficiency or is severely malnourished, a third dose must be given 2–4 weeks after the second dose.

Hepatic impairment: supplementation may be required in children with liver disease, particularly cholestatic liver disease, due to malabsorption of fat-soluble vitamins. In those with complete biliary obstruction, IM dosing may be appropriate.

Pregnancy: Contraindicated

Adverse effects: No serious or irreversible adverse effects are seen in recommended doses.

High intake may cause birth defects (if taken during pregnancy), transient increased intracranial pressure in adults and older children or a tense and bulging fontanelle in infants (with high dosage), massive overdose can cause rough skin, dry hair, enlarged liver, raised erythrocyte sedimentation rate, raised serum calcium and raised serum alkaline phosphatase concentrations.

Interaction with other medicines with other medicines: There are no known interactions where it is recommended to avoid concomitant use.

Thiamine (Vitamin B1)

ATC code: A11DA01

Tablet, 50 mg (HCl), LOU 4

Injection, 100 mg/mL 2-mL vial

Indications and dose

Adult

For the prevention and treatment of vitamin B1 deficiency or beriberi, IM or slow IV infusion: 10–20 mg 3 times/day for up to 2 weeks, then

oral maintenance with therapeutic multivitamin preparation containing 5–10 mg thiamine daily for 1 month: 5–10 mg orally 3 times/day

Thiamine deficiency, treatment and prophylaxis, oral:

Dietary supplement, 100 mg daily

Recommended dietary allowance:

men, 1.2 mg/day,

women, 1.1 mg/day,

pregnancy and breastfeeding, 1.4 mg/day

Paediatric

Prevention of thiamine deficiency, Oral:

Infant: 0.3–0.5 mg/day.

Child: 0.5–1 mg/day.

Treatment of thiamine deficiency (beriberi), Oral:

Child: 10–50 mg/dose daily for 2 weeks, then 5–10 mg/dose daily for 1 month.

Recommended dietary intake.

Infant: 0.03 mg/kg.

Child 1–3 years: 0.5 mg.

4–8 years: 0.6 mg.

9–12 years: 0.9 mg

Renal impairment: dose reduction not necessary.

Hepatic impairment: dose reduction not necessary.

Interaction with other medicines with other medicines (*indicates serious): There are no known interactions where it is recommended to avoid concomitant use.

Notes:

» For smaller doses, the tablet may be dispersed in a small amount, e.g., 5 mL of clean water to produce a solution (10 mg/mL) that then allows the appropriate volume to be given. Discard any remaining solution and use a new tablet for each dose.

Thiamine (Vitamin B1)

ATC code: A11DA01

IV infusion, 1 pair is one 5-mL amp containing thiamine 250 mg, riboflavin (vitamin B2) 4 mg and pyridoxine (vitamin B6) 50 mg, and one 5-mL amp containing ascorbic acid (vitamin C) 500 mg, nicotinamide (vitamin B3) 160 mg and glucose 1000 mg, LOU 4

Indications and dose

Adult

Treatment of suspected or established Wernicke's encephalopathy by IV infusion: 2–3 pairs three times daily for 3–5 days followed by one pair once daily for a further 3–5 days or for as long as improvement continues

Alcohol withdrawal syndrome (adjunct) (off-label use), prevention of Wernicke encephalopathy, sepsis (severe) or septic shock (off-label use), IV infusion: 1 pair every 12 hours over 30 minutes for 4 days or until ICU discharge,

administer in combination with IV hydrocortisone.

Paediatric: No doses listed for indication

Hepatic and renal Impairment: No dosage adjustment.

Notes:

Empirical treatment to prevent Wernicke-korsakoff syndrome in alcoholics and patients with altered mental status of unknown aetiology, also used in malnourished patients and as adjunct treatment in ethylene glycol (ethanol) poisoning in patients with properly diagnosed vitamin B deficiency

Parenteral administration is preferred in inpatient management of alcohol withdrawal, particularly for patients with malabsorption, poor nutritional status, or severe complications of alcohol withdrawal

Should be diluted in 50 to 100 mL of 0.9% sodium chloride and administered over 30 minutes.

Vitamin B12 (Cobalamin)

ATC code: B03BA01

Tablet, 500 micrograms LOU 3

Injection, 1000 micrograms/mL 1 mL amp LOU 4

Indications and dose

Adult

Cobalamin deficiency, treatment, oral: 500 micrograms daily

Cobalamin deficiency, prophylaxis, oral: 1000 micrograms once daily

Hyperhomocysteinemia, oral: 500 micrograms/day with folic acid

Addisonian pernicious anaemias and other macrocytic anaemias without neurological involvement, IM: Initially 250 to 1000 micrograms on alternate days for one or two weeks, then 250 micrograms weekly until the blood count is normal

Maintenance: 1000 micrograms every two to three months

Addisonian pernicious anaemia and other macrocytic anaemias with neurological involvement, IM: Initially:1000 micrograms on alternate days as long as improvement is occurring.

Maintenance:1000 micrograms every two of three months.

Prophylaxis of macrocytic anaemia associated with vitamin B12 deficiency resulting from gastrectomy, some malabsorption syndromes and strict vegetarianism, IM: 1000 micrograms every two or three months.

Tobacco amblyopia and Leber's optic atrophy, IM: Initially:1000 micrograms daily for two weeks then twice weekly as long as improvement is occurring.

Maintenance: 1000 micrograms every one to three months as required.

Paediatric

Child all ages:

Addisonian pernicious anaemias and other macrocytic anaemias without neurological involvement, IM: Initially 250 to 1000 micrograms on alternate days for one or two weeks, then 250 micrograms weekly until the blood count is normal

Maintenance: 1000 micrograms every two to three months

Addisonian pernicious anaemia and other macrocytic anaemias with neurological involvement, IM: Initially:1000 micrograms on alternate days as long as improvement is occurring.

Maintenance:1000 micrograms every two of three months.

Prophylaxis of macrocytic anaemia associated with vitamin B12 deficiency resulting from gastrectomy, some malabsorption syndromes and strict vegetarianism, IM: 1000 micrograms every two or three months.

Tobacco amblyopia and Leber's optic atrophy, IM: Initially:1000 micrograms daily for two weeks then twice weekly as long as improvement is occurring.

Maintenance: 1000 micrograms every one to three months as required.

Contraindications

Hypersensitivity to cobalt, vitamin B12, or any component of the product

Precautions

Concomitant use: concomitant use with bone marrow suppressants (e.g., chloramphenicol) may blunt therapeutic response.

Endocrine and metabolic: irreversible neurological damage may occur if vitamin B12 deficiency is inadequately controlled for more than 3 months, monitoring recommended and consider switching to IM route for patients taking other dose forms.

Endocrine and metabolic: folate deficiency, previously unrecognized, may be masked by doses exceeding 10 micrograms/day, cyanocobalamin is not a substitute for folic acid, monitoring recommended.

Endocrine and metabolic: in patients with concurrent iron or folic acid deficiency, therapeutic response may be blunted, monitoring recommended.

Hematologic: when severe megaloblastic anaemia is treated intensely with cyanocobalamin, hypokalaemia, thrombocytosis, and sudden death may occur, monitoring recommended

Hematologic: polycythaemia vera symptoms, may be suppressed by vitamin B_{12} deficiency and treatment may unmask condition, if polycythaemia vera occurs, further evaluation may be required (intranasal)

Immunologic: anaphylactic shock and death have been reported with parenteral vitamin B12 administration, if hypersensitivity is suspected, consider an intradermal test dose

Immunologic: in patients with infection, therapeutic response may be blunted, monitoring recommended

Ophthalmic: patients with early leber disease (hereditary optic nerve atrophy) may have increased risk for severe, sudden optic atrophy, use not recommended and consider alternative vitamin B12 therapy

Renal (injection route): in patients with renal impairment, prolonged parenteral administration increases risk of aluminium toxicity, particularly in premature infants.

Renal: in patients with uraemia, therapeutic response may be blunted, monitoring recommended

Respiratory: patients with nasal pathology and chronic nasal symptoms have potential for erratic or blunted absorption, monitoring recommended

Special populations (injection route): increased risk of fatal gasping syndrome in premature infants since injectable product contains benzyl alcohol.

Pregnancy category: foetal risk cannot be ruled out.

Breastfeeding infant risk is minimal.

Adverse effects: Common: Neurologic: Asthenia, headache, paraesthesia

Serious: Cardiovascular: congestive heart failure, pulmonary oedema, thrombosis

Immunologic: anaphylaxis

Ophthalmic: optic atrophy

Interaction with other medicines: Moderate, chloramphenicol (probable)

Note:

» Prior to treatment, obtain haematocrit, reticulocyte count, vitamin B12, folate, and iron levels. Consider the potential for concomitant drugs to interfere with vitamin B12 and folate diagnostic blood assays. In patients with suspected cobalamin hypersensitivity, consider administering an intradermal test dose of parenteral vitamin B12 prior to use.

Zinc Sulphate

ATC code: A12CB01

Tablet (dispersible), 20 mg, LOU 2

Indications and dose

Adult

Mild Zinc deficiency, oral: two to three times the RDA of zinc for 6 months.

Moderate to severe deficiency Zinc deficiency, oral: four to five times the RDA for 6 months.

For diarrhea: To prevent diarrhea in infants, pregnant women have used 15 mg of zinc, with or without 60 mg of iron and 250 micrograms of folic acid, starting 10–24 weeks into pregnancy through one month after giving birth.

Paediatric

Adjunct in management of diarrhoea, oral:

Infant under 6 months: 10 mg (elemental zinc) daily for 10–14 days,

Child 6 months–5 years: 20 mg (elemental zinc) daily for 10–14 days.

Administration:

Zinc sulphate tablets may be dispersed in breastmilk, in oral rehydration solution, or in water on a small spoon, older children may chew the tablets or swallow them with water.

Precautions: acute renal failure (may accumulate). Zinc is likely safe when taken in the RDA but may be harmful when taken in high amounts

Renal impairment Accumulation may occur in acute renal failure.

Pregnancy: It is relatively safe when taken in the RDA: Crosses placenta, risk theoretically minimal, but no information available.

Breastfeeding Present in milk, risk theoretically minimal, but no information available.

Adverse effects: abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, gastritis, irritability, headache, lethargy.

Interactions with other medicines:

Tetracycline Antibacterials: Zinc may reduce the absorption of concurrently administered tetracyclines, also the absorption of zinc may be reduced by tetracyclines, when both are being given an interval of at least three hours should be allowed.

Quinolone Antibacterials: Zinc may reduce the absorption of quinolones, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin.

Calcium Salts: The absorption of zinc may be reduced by calcium salts.

Iron: The absorption of zinc may be reduced by oral iron, also the absorption of oral iron may be reduced by zinc.

Penicillamine: The absorption of zinc may be reduced by penicillamine, also the absorption of penicillamine may be reduced by zinc.

Trientine: The absorption of zinc may be reduced by trientine, also the absorption of trientine may be reduced by zinc.

33. Preparations For Clinical Nutrition Management

33.1. Feeds For Special Medical Purposes

33.1.1. Parenteral Feeds

33.1.1.1. Background Information

PN is essential when patients cannot meet the nutrient requirements enterally (oral or tube feeding): it is administered intravenously either as total parenteral or partial (supplemental) nutrition. Parenteral formulations solutions contain amino acids, glucose, fat emulsions, electrolytes, trace elements, and vitamins, they can be presented as combination or single nutrients. The micronutrients need to be added daily to the parenteral solutions to avoid deficiencies especially for those on TPN.

Baseline biochemical tests such as renal, liver function and acid-base balance needs should be done and deficit corrected prior to initiation of PN.

PN solutions vary in their amino acids composition. The energy to protein nitrogen ratio should be maintained in a ratio of 150–250 kcal/g of protein nitrogen. Energy requirements must be met if amino acids are to be utilized for tissue maintenance. The glucose strength varies from 5% to 50%. Sufficient amount of phosphate in PN is crucial to prevent hypophosphatemia as a result of glucose phosphorylation. Fat emulsions provide essential fatty acids (linoleic acid and alpha-linolenic acid) and are usually energy dense, with similarity in plasma osmolarity and pH. A fat emulsion with balanced LCT, medium-chain triglyceride (MCT), Olive oil and fish oils are associated with less liver dysfunction and help attenuate the inflammatory response.

Indications:

For patients in whom EN is not feasible or not tolerated, those who cannot meet >60% of their caloric need and in severe or prolonged disorders of the GIT. Some of scenarios where PN would be used include but not limited to

- Preterm babies
- Babies with Necrotizing enterocolitis
- Peritonitis
- High output enterocutaneous fistula
- Some critically ill patients such as trauma, burns
- Patients with acute abdomen
- Intestinal perforation and obstruction

Route:

PN should be infused through an aseptically inserted CVC or Peripheral venous catheter. All PN solutions should be given via a dedicated IV line. PN solutions **exceeding** 900 mOsm/L should **ONLY** be infused via a CVC.

Complications:

can result in both metabolic and nutritional complications such as fluid overload/dehydration, electrolyte imbalance, hyperglycaemia/hypoglycaemia, over feeding, re-feeding syndrome, nutrient deficiency especially micronutrients, and hepatobiliary dysfunction.

Dose: Majorly dependent on individual patient-related factors.

Adult

25 – 30 kcal/kg/day or as per nutritional status of the patient.

Glucose minimum of 150–200 g to prevent ketone production

Protein 0.8–2 g/kg/day

Lipid 0.7–1.5g/kg/day

Fish oil (omega 3) 0.1–0.2 g/kg/day

Paediatric

Macronutrient Guidelines in Paediatric PN				
	A.A.P.		A.S.P.E.N.	
Protein	10 to 20 kg	1 to 2.5 g/kg	>10 kg or 1 to 10 yrs	1 to 2 g/kg
	>20 kg	0.8 to 2 g/kg	11 to 17 yrs	0.8 to 1.5 g/kg

Energy/Caloric	10 to 20 kg	60 to 90 kcal/kg	>1 to 7 yrs	75 to 90 kcal/kg
	>20 kg	30 to 75 kcal/kg		50 to 75 kcal/kg
			>12 to 18 yrs	30 to 50 kcal/kg
Fluid	1 to 10 kg 100 mL/kg, 11 to 20 kg 50 mL/kg,>20 kg 20 mL/kg			
Carbohydrate (Dextrose)	10 to 20 kg	8 to 28 g/kg	Carbohydrates should comprise 40 to 60% of total caloric intake	
	>20 kg	5 to 20 g/kg		
IV fat emulsion	>10 kg	1 to 3 g/kg	The minimum fat requirements is determined by essential fatty acid need, and the daily maximum of 50 to 60% of energy	

Administration:

PN solutions should be infused slowly to avoid complications. Ensure that the glucose infusion does not exceed 5 mg/kg/min in adults, 8 mg/Kg/min in preterm and 12 mg/Kg/min in term babies with frequent glucose monitoring at least 6 hourly.

Compatibility with the infusion solution must be ascertained before adding supplementary preparations.

Precautions:

There is need for regular monitoring of the micronutrients (especially Manganese, Folic acid and vitamin B12) on patients on long-term TPN.

Care should be taken when interpreting blood gases and calcium especially when samples are drawn before fat has been cleared in patients with impaired fat metabolism.

Ensure compatibility of the PN additives with PN solutions prior to mixing them.

Use within 48 hrs or follow the manufacturer's instructions to ensure potency.

For patients exhibiting hyperglycaemia insulin infusion might be warranted.

Note:

- PN solutions should always be administered together with the micronutrients and trace elements to ensure they are nutritionally complete
- PN formulations are available in different volumes ranging from 100 mL to 2 L. The trace elements and vitamins are mostly available in smaller volumes of 10 mL ampoules.

Amino Acids

ATC code: B05BA01

Solution for IV infusion amino acid + glutamine per 100-mL bottle, LOU 4

Solution for IV infusion 5–6% with amino acid with glucose (100-mL bottle), LOU 4

Solution for IV infusion 7% (500-mL bottle), LOU 4

Solution for IV infusion 8% (500-mL bottle), LOU 4

Solution for IV infusion 10% with electrolytes (500-mL bottle), LOU 4

Indications and dose

For gut resuscitation: Solution for IV infusion amino acid + glutamine per 100 mL

For specialized use in children, preterm, neonates in pancreatic failure and hepatic disease in infants: Solution for IV infusion 5–6% with glucose

For specialized use in renal failure in adults and children: Solution for IV infusion 7% Containing amino acids only

For specialized use Hepatic failure/disease in adults and children: Solution for IV infusion 8% (500-mL bottle). Containing amino acids only.

For Severe liver insufficiency and imminent or manifest hepatic encephalopathy. Increased protein needs for adults and children: Solution for IV infusion 10% with electrolytes (500-mL bottle)

Adults

The patient's protein needs determine the protein concentration to use, and the underlying disease state determines the composition of amino acid. A nonprotein kcal to nitrogen ratio of 80:1(severely stressed patients) to 150:1(unstressed patients) is used.

Ranges from 0.6 to 1.6 g/kg/day and not to exceed an infusion rate of 0.1 g/kg

Paediatric

3 to 4 g/kg/day for preterm and term infants less than 1 month of age,

2 to 3 g/kg/day for paediatric patients 1 month to less than 1 year of age,

1 to 2 g/kg/day for paediatric patients 1 to 10 years of age and

0.8 to 1.5 g/kg/day for paediatric patients greater than 10 to less than 17 years of age

Flow Rate:

Treatment of Hepatic Coma:

In hepatic encephalopathy, it is recommended to start the infusion of amino acid solution 10% at an increased rate, until onset of the effect, e.g., for a patient weighing 70 kg:
1st-2nd hour: 150 mL/hour (2 mL/kg body weight/hour), corresponding to approximately 50 drops/min,
3rd-4th hour: 75 mL/hour (1 mL/kg body weight/hour), corresponding to approximately 25 drops/min, from
5th hour: 45 mL/hour (0.6 mL/kg body weight/hour), corresponding to approximately 15 drops/min.

Contraindications:

Disorders of amino acid metabolism of other than hepatic origin, life-endangering unstable circulation (shock), acidosis, hyper hydration, hypokalemia, hypernatremia.
Because of the particulars of its composition, amino acid solution 10% may cause marked metabolic disturbances if given for other reasons than stated under Indications.

Precautions: Renal impairment,Hepatic impairment
Paediatric Use: Neonates, especially premature infants with low birth weight, are at increased risk of developing hypo- or hyperglycemia and therefore need close monitoring during treatment with IV glucose solutions to ensure adequate glycemic control in order to avoid potential long term adverse effects

Adverse effects:

Pulmonary embolism due to pulmonary vascular precipitates, hypersensitivity reactions, refeeding syndrome, hyperglycemia or hyperosmolar hyperglycemic state

vein damage and thrombosis, hepatobiliary disorders, hepatobiliary disorders are known to develop in some patients without preexisting liver disease who receive PN, including cholecystitis, cholelithiasis, cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure.

Risk of PN associated liver disease

Electrolyte imbalance and fluid overload

Phosphorus deficiency may lead to impaired tissue oxygenation and acute hemolytic anemia. Relative to calcium, excessive phosphorus intake can precipitate hypocalcemia with cramps, tetany and muscular hyperexcitability.

Interaction with other medicines:

Microbial contamination and physicochemical incompatibility, it is not recommended that any additives should be incorporated into the solutions, but should preferably be given in standard carbohydrate or electrolyte solutions. However, if admixture with amino acid solution 10% is essential, then the compatibility of the additives must be checked before administration

Some additives may be incompatible. Consult with pharmacist. When introducing additives, use aseptic techniques. Mix thoroughly.

Notes:

- Amino acid therapy is not a substitute for established therapeutic measures, e.g., purging, administration of lactulose and/or gut-sterilizing antibiotics, in the treatment of hepatic encephalopathy.
- Clinical supervision should include regular checks of fluid balance and serum electrolytes. Electrolytes are to be supplemented as required.
- Monitor regularly liver function parameters in patient with compensated hepatic insufficiency. Control serum electrolytes, serum osmolality, water balance, acid-base status and liver function tests (alkaline phosphatase, ALT, AST) and possible symptoms of hyperammonaemia.

Combined amino acid and glucose for Central Administration-Two chamber bag for central administration

ATC code: B05BA10

Solution for IV infusion, 1 L, LOU 5

(Containing carbohydrates and protein, with electrolytes, fat free)

Indications and dose

For use in management of pancreatic failure and hepatic disease in both adults and children.

Patients who need short-term PN when EN is contraindicated.

Supplement oral/EN when inadequate.

Adult

Should be individualized to suit patient's requirements.

Upper limit of 40 mL/kg/day

Paediatric: Dose depends on the weight and age of the child.

Method of Administration:

Should ONLY be administered as a slow continuous IV infusion via central line over 12–24 hours.

Aseptic precautions MUST be observed when mixing and administration to the patient.

Frequent continuous monitoring of the various biochemical markers is warranted.

Once it has been premixed use the mixture within 24–48hours and any remaining content should be discarded.

Contraindications:

Severe haemodynamic instability such as in shock and cardiac failure, severe metabolic acidosis, hyperkalemia, hypersensitivity to one or more amino acids/dextrose, neonates and infants, severe renal

failure without renal replacement therapy, severe hepatic insufficiency

Precautions:

Use cautiously in patients with diabetes mellitus, renal failure, metabolic syndrome, impaired fat metabolism and sepsis.

The infusion MUST be stopped immediately should there be any signs of an adverse reaction.

Adverse effects: Rare: Allergic anaphylactic reaction, hypertriglyceridaemia, coagulopathy, hyperglycaemia, dyspnea, tachycardia, hepatobiliary disorders, extravasation, electrolyte imbalance

Interaction with other medicines: Efficacy of glycosides can be reduced due to the potassium content.

Note:

» Adjust infusion rate in cases of hyperglycaemia

Combined amino acid, glucose and lipids with medium chain Triglycerides (MCT) / Long chain Triglycerides (LCT) - Three Chamber Bag For Central Administration

ATC code: B05BA10

Solution for IV infusion,1 L and 2 L, LOU 5

Containing carbohydrates, fat (LCT and MCT) and protein, with electrolytes.

Indications and dose:

For use in nutrition management of adult and paediatric patients on long-term PN support where GIT in non-functional, short bowel syndrome,

Where a CVC is present.

Supplement oral/EN when inadequate.

Adult

Should be individualized to suit patient's requirements.

Do not exceed 40 mL/kg/day

Paediatric

Not recommended for use in paediatric patients below 2 years as it does not meet their nutritional requirements.

The safety and effectiveness in paediatric patients has not been established.

Method of Administration:

Should ONLY be administered as a slow continuous IV infusion via central line over 12 to 24hours.

Aseptic precautions MUST be observed when mixing and administration to the patient.

Frequent continuous monitoring of the various biochemical markers is warranted.

Once it has been premixed use the mixture within 24 to 48hours and any remaining content should be discarded.

Contraindications:

Severe haemodynamic instability such as in shock and cardiac failure, severe metabolic acidosis, hyperkalemia, hypersensitivity to one or more amino acids/dextrose, neonates and infants, severe renal failure without renal replacement therapy, severe hepatic insufficiency, severe coagulopathy, uncontrolled hyperglycaemia

Precautions:

Use cautiously in patients with diabetes mellitus, renal failure, metabolic syndrome, impaired fat metabolism and sepsis.

The infusion MUST be discontinued immediately should there be any signs of an adverse reaction.

Adverse effects: Rare: Allergic anaphylactic reaction, hypertriglyceridaemia, coagulopathy, hyperglycaemia, dyspnoea, tachycardia, hepatobiliary disorders, extravasation, electrolyte imbalance, fat overload syndrome, Nausea, vomiting, fever, chills

Interaction with other medicines: Efficacy of glycosides can be reduced due to the potassium content.

Notes:

» Renal replacement therapy: monitor potassium and phosphate.

» Adjust infusion rate in cases of hyperglycaemia

Combined amino acid, glucose and lipids with medium chain Triglycerides (MCT) / Long chain Triglycerides (LCT) - Three Chamber Bag for Peripheral Administration

ATC code: B05BA10

Solution for IV infusion, 500 mL, 1 L, 1.5 L, 2 L, LOU 4

(Containing carbohydrates, fat (LCT and MCT) and protein, with electrolytes).

Indications and dose

For use in management of adult and paediatric patients on short term PN support where enteral route is not feasible, e.g., grade IV dysphagia, obstructive upper GI tumours.

Where a CVC is contraindicated

Supplement oral/EN when inadequate.

Adult

Should be adjusted to suit patient's individual requirements.

Max 40 mL/kg/day

Paediatric: Dose depends on weight and age of the child

Method of Administration:

Should be administered as a slow continuous infusion via a peripheral or central line over 12 to 24hours.

Aseptic precautions MUST be observed when mixing and administration to the patient.

Frequent continuous monitoring of the various biochemical markers is warranted.

Once it has been premixed use the mixture within 24 to 48hours and any remaining content should be discarded.

Contraindications:

Severe haemodynamic instability such as in shock and cardiac failure, severe metabolic acidosis, hyperkalemia, hypersensitivity to one or more amino acids/dextrose, neonates and infants, severe renal failure without renal replacement therapy, severe

hepatic insufficiency

Precautions:

Use cautiously in patients with diabetes mellitus, renal failure, metabolic syndrome, and sepsis

The infusion MUST be stopped immediately should there be any signs of an adverse reaction.

Adverse effects: Rare: Allergic anaphylactic reaction, hypertriglyceridaemia, coagulopathy, hyperglycaemia, dyspnea, tachycardia, hepatobiliary disorders, extracasation, electrolyte imbalance

Interaction with other medicines: Efficacy of glycosides can be reduced due to the potassium content.

Notes:

- Renal replacement therapy: Stop administration during hemodialysis and continue after dialysis session.
- Adjust infusion rate in cases of hyperglycaemia

Fat Emulsion

ATC code: B05BA02

20% fat emulsion for IV infusion, 100 mL and 500 mL, LOU 4

Indications and dose

Supply of energy and essential fatty acids and omega-3 fatty acids to patients, as part of a PN regime including hyper-metabolic patients, or patients with volume or carbohydrate restrictions.

Adults

Standard Dose: 1 to 2 g fat/kg body weight/day, corresponding to 5 to 10 mL/kg body weight/day.

To prevent fatty acid deficiency give 500 mL of 10% lipids once or twice a week.

Administration

Recommended infusion rate: 0.125 g fat/kg body weight/hour, not exceed 0.15 g fat/kg body weight/hour.

It is recommended not to exceed a daily dose of 2.5 g fat/kg body weight/day.

The rate of infusion should not exceed 0.125 g fat/kg body weight/hour In premature and low birth weight neonates.

Should be infused continuously over about 24 hours.

Lipids are administered 2 to 3 times per week, but can be provided daily. Infusion times of 4–6 hours for 10% lipids and 8 to 12 hours for 20% lipids are recommended.

coagulation disorders, renal insufficiency without access to hemofiltration or dialysis, acute shock, general contraindications to infusion therapy: Acute pulmonary oedema, hyperhydration, decompensated cardiac insufficiency.

Adverse effects*:*

Respiratory, thoracic and dediastinal disorders: Rare: dyspnoea.

GI disorders: lack of appetite, nausea, vomiting.
Vascular Disorders: Rare: hypotension, hypertension.

General disorders and administration site conditions: Common: Slight increase in body temperature.

Reproductive System: Priapism.

Should these undesirable effects occur or should the triglyceride level during infusion rise >3 mmol/L, the treatment should be stopped or, if necessary, continued at a reduced dosage.

Interaction with other medicines:

Heparin given in clinical doses causes a transient increase in lipoprotein lipase release into the circulation. This may initially result in increased plasma lipolysis, followed by a transient decrease in triglyceride clearance.

Soya bean oil has a natural content of vitamin K1 that it is not expected to significantly influence the coagulation process in patients treated with coumarin derivatives.

Fat Soluble Vitamins For IV Infusion

ATC code: B05XC

Lipid soluble vitamins for IV infusion for adults, 10 mL, LOU 4

Lipid soluble vitamins for IV infusion for paediatric use, 10 mL, LOU 5

Indications and dose

Indicated as a supplement in complete IV nutrition to meet the daily requirements of fat-soluble vitamins for both adults and children.

Adult

Based on expert opinion. A general recommendation is given in the table below. Should be given daily except for vitamin K which should be given weekly parenterally or intramuscularly, at a dose of 2 to 4 mg/week, depending on PT. A long PT indicates an increased vitamin K need.

Paediatric

Neonates and Infants: Initial Dose: 0.5 to 1 g fat/kg body weight/day followed by a successive increase by 0.5 to 1 g fat/kg body weight/day up to 3 g fat/kg body weight/day.

The rate of infusion should not exceed 0.125 g fat/kg body weight/hour In premature and low birth weight neonates.

Children: It is recommended not to exceed a daily dose of 3 g fat/kg body weight/day.
The daily dose should be increased gradually during the 1st week of administration.
The infusion rate should not exceed 0.15 g fat/kg body weight/hour.

Contraindications:
Hypersensitivity to fish, egg, soya or peanut protein.

Severe hyperlipidemia, liver insufficiency, blood

Paediatric

Recommended doses for parenteral supply of fat soluble and water-soluble vitamins for preterm infants, infants and children.

	Preterm	Infants to 12 months	Children and adolescent 1 to 18 years
Vitamin A[1]	700 to 1500 IU/kg/day (227 to 455 ug/kg/day)	150 to 300 micrograms/kg/day or 2300 IU/day (697 micrograms/day)	150 micrograms/day
Vitamin D[2]	200 to 1000 IU/day or 80 to 400 IU/kg/day	400 IU/day or 40 to 150 IU/kg/day	400 to 600 IU/day
Vitamin E[3]	2.8 to 3.5 mg/kg/day or 2.8 to 3.5 IU/kg/day	2.8 to 3.5 mg/kg/day or 2.8 to 3.5 IU/kg/day	11 mg/day or 11 IU/day
Vitamin K	10 ug/kg/day (recommended, but currently not possible)[4]	10 micrograms/kg/ day (recommended, but currently not possible)4	200 micrograms/day
Vitamin C	15 to 25 mg/kg/day	15 to 25 mg/kg/day	80 mg/day
Thiamine	0.35 to 0.50 mg/kg/day	0.35 to 0.5 mg/kg/day	1.2 mg/day
Riboflavin	0.15 to 0.2 mg/kg/day	0.15 to 0.2 mg/kg/day	1.4 mg/day
Pyridoxine	0.15 to 0.2 mg/kg/day	0.15 to 0.2 mg/kg/day	1 mg/kg/day
Niacin	4 to 6.8 mg/kg/day	4 to 6.8 mg/kg/day	17 mg/day
Vitamin B12	0.3 micrograms/kg/day	0.3 micrograms/kg/day	1 microgram/day
Pantothenic acid	2.5 mg/kg/day	2.5 mg/kg/day	5 mg/day
Biotin	5 to 8 micrograms/kg/day	5 to 8 micrograms/kg/day	20 micrograms/day
Folic acid	56 micrograms/kg/day	56 micrograms/kg/day	140 micrograms /day

Source: ESPGHAN/ESPEN/ESPR/CSPEN guidelines on paediatric PN

Administration:

Whenever possible water and lipid soluble vitamins should be added to the lipid emulsion or a mixture containing lipids one hour to commencement of the feeding to increase vitamin stability.

Contraindications:

Pre-existing hyper-vitaminosis.

Hypersensitivity to eggs, soya

Disturbances in lipid metabolism

Acute shock.

Precautions:

Doses recommended are insufficient to correct severe deficiency states and may be insufficient in patients with markedly increased requirement.

Fat soluble vitamins can become toxic, and are provided in amounts equal to the RDA, except for vitamin K which may interfere with anticoagulant medications

Patients for whom TPN is continued for prolonged periods, periodic monitoring of blood levels of vitamins, particularly A and D, should be considered.

In patients receiving TPN, routine supplementation with both fat-soluble and water-soluble vitamins is recommended to prevent deficiency states and to obviate the need to speculate on individual vitamin status.

1 microgram RAE (retinol activity equivalent) = 1 microgram all-trans retinol = 3.33 IU vitamin A. In infants an intravenous vitamin A supply of about 920 IU/kg per day together with the water-soluble mixture or 230e500 IU/kg per day with the lipid emulsion are often used. Since losses are quite variable and losses are higher in the water-soluble mixture, the amount delivered to the patient may be estimated to be approx. 300 to 400 IU/kg per day for both options. Recommended daily parenteral dose for term neonates is 2300 IU and for preterm neonates approximately 700 to 1500 IU/kg.

2 Recommended doses of vitamin D for preterm and term infants are given not only as absolute quantity but also as per kg body weight.

3 Upper limit in preterm and term infants should not exceed 11 mg/day; however, higher doses of vitamin E per day after using the new lipid emulsions and multivitamins together have been shown with apparently no harmful effect. Upper limit for children and adolescents should be established in further well-designed studies.

4 Current multivitamin preparations supply higher vitamin K amounts without apparent adverse clinical effects. Dose is independent on local policy of VKDB prevention.

However, daily vitamin requirements must be calculated to avoid overdosage and toxic effects, especially with regards to vitamins A and D, and particularly in paediatric patients.

Hypervitaminosis A is characterised by fatigue, irritability, anorexia and loss of weight, vomiting and other GI disturbances, polyuria and cracking and bleeding lips. Hypervitaminosis D is a metabolic bone disease characterized by hypercalciuria, intermittent hypercalcaemia, osteomalacia and bone pain.

Adult formulations containing propylene glycol and polysorbate additives are not recommended for use in infants because of concerns about potential toxicity

Use in pregnancy: The recommended doses may be insufficient in pregnancy and during breastfeeding due to the patient's altered vitamin requirements for example, increased requirements for vitamins D and E.

Adverse effects: No adverse effects have been reported.

Interaction with other medicines:

The solution contains vitamin K1 which may interact with anticoagulants of the coumarin type.

Some vitamins may adhere to the tubing and/or be affected by light, humidity and temperature, infusion rate therefore, the actual amount of vitamins delivered to the patient may be much lower than the intended dose. Adjusting doses may be necessary.

Other drugs and solutions should not be added to the solution.

Trace Elements, Adult

ATC code: B05XA31

Solution for IV infusion, 10 mL, LOU 4

Containing zinc, copper, manganese and selenium trace elements indicated as a source of these nutrients when oral or EN is not possible, insufficient or contraindicated in adults and children weighing more than 10 kg.

Indications and dose

It is part of an IV nutrition regimen, to cover basal or moderately increased trace element requirements in PN in both adults and children respectively.

To be added for patients receiving TPN and those at risk of developing trace element deficiency.

Adult

Requirements are based on monitoring results and adjusted based on serum concentrations.

(Refer to table on general recommendations for vitamins and trace elements for adults)

Zinc may be required in higher dosage to promote wound healing

Modify dosage for patients with cholestasis, biliary dysfunction or cirrhosis while monitoring during long term administration.

Monitor serum Zinc, copper, selenium and manganese whole blood concentrations.

Paediatric

1 mL/kg per day for paediatric patients weighing less than 15 kg.

For paediatric patients weighing more than 15 kg, give 15 mL/day

The solution may not provide the recommended daily dosage of zinc (in heavier patients in some weight bands), copper or selenium. Additional supplementation using single trace element products may be needed for these patients.

Administration:

To be infused into the parenteral admixture prior to PN administration.

Contraindications:

Wilsons Disease.

Not recommended for patients who may require a lower dosage of one or more of the individual trace elements.

Accumulation in the basal ganglia

Precautions:

In children, it should be used with caution when the excretion in bile is reduced, particularly in cholestatic liver disease or when the urinary excretion is markedly reduced. Such patients require careful biochemical monitoring.

If the treatment is continued for >4 weeks, control of manganese level is required. Free iron can increase susceptibility to infections

Critically ill or malnourished patients may have no bone marrow response to iron.

Copper supplementation must be administered with caution to avoid toxicity.

Adverse effects:

With other components of PN solutions,

Pulmonary embolism, thrombosis

Neurologic toxicity with manganese

Hepatic accumulation of copper and manganese

Hypersensitivity reactions with zinc and copper

Aluminium toxicity

Interaction with other medicines: None known

Note:

» Trace elements concentration may vary depending on the assay used and the laboratory reference range.

Trace Elements, Paediatric

ATC code: B05XA31

Solution for IV infusion, 10 mL, LOU 4

Containing zinc chloride, copper chloride, manganese chloride, sodium selenite, sodium fluoride, potassium iodide

Indications and dose

Paediatric

Indicated for use in infants and children requiring IV nutrition to supply basal requirements of trace elements

Child ≤15kg weight: 1 mL/kg per day

Child > 15kg weight: 15 mL/day

Should be administered diluted in the PN solution

Contraindications: Wilson's disease

Precautions:

Should be used with caution in patients with impaired biliary and/or renal function in whom excretion of trace elements may be significantly decreased

Hepatic impairment especially cholestasis

Manganese levels should be checked for patients using the trace elements for over four weeks

Adverse effects: None known

Interaction with other medicines: None Known

Water Soluble Vitamins

ATC code: B05XC

Water-soluble vitamins for IV infusion for adults and children,10 mL, LOU 4

Indications and dose

Intended as a supplement in IV nutrition in order to meet the daily requirements of the water-soluble vitamins in adults, adolescents, children and infants.

Adults

Individualised based on need

(Refer to general recommendations for parenteral vitamins and trace elements)

Paediatric

Children and infants weighing less than 10 kg: 1 mL per kg body weight per day.

Children weighing over 10kg: Refer to general recommendations for parenteral vitamins and trace elements

Administration:

Added to PN admixtures containing carbohydrates, lipids, amino acids, electrolytes, and trace elements, provided that compatibility and stability have been confirmed.

It must not be given undiluted.

The reconstituted solution should be added to the infusion solution under sterile conditions, immediately before the start of the infusion and used within 24 hours.

Clear admixtures (e.g., glucose solution or water for injection) containing the water soluble vitamins should be protected from light.

Contraindications:

Known hypersensitivity to any of the components, for example, thiamine or methyl hydroxybenzoate.

Water-soluble vitamins are provided at levels greater than the RDA since rapid administration exceeds renal threshold and therefore increases urinary losses

Precautions:

Administering folic acid may obscure pernicious anemia.

Doses recommended are insufficient to correct severe vitamin deficiency states and may be insufficient in patients with markedly increased vitamin requirements.

In patients receiving TPN, routine supplementation with both fat-soluble and water-soluble vitamins is recommended to prevent deficiency states and to obviate the need to speculate on individual vitamin status.

Daily vitamin requirements must be calculated to avoid overdosage and toxic effects, especially with regards to vitamins A and D, and particularly in paediatric patients.

In patients for whom TPN is continued for prolonged periods (months or years), periodic monitoring of blood vitamin levels should be considered.

To prevent excessive excretion of water-soluble vitamins, and for reasons of safety, daily dosage should be administered over a number of hours.

Adverse effects:

Allergic reactions including anaphylactic reactions may occur in patients hypersensitive to any component in the preparation, for example, folic acid, methyl hydroxybenzoate or thiamine.

Anaphylactoid reactions following repeated injection of preparations containing thiamine.

Flushing, itching or burning of the skin may occur in patients susceptible to the effects of nicotinamide.

Adverse reactions that may be expected based on experience with other water-soluble vitamin compounds administered intravenously include allergic reactions, including anaphylaxis, dermatological reactions including flushing, erythema, pruritus, and CNS reactions including headache, dizziness, and agitation.

Interaction with other medicines:

Vitamin B6 can reduce the effect of levodopa.

Folic acid may lower the serum concentration of phenytoin.

Other drugs should not be added to the water-soluble solution due to the possibility of physical incompatibilities.

Recommended doses, toxicity and adverse effects for IV vitamins and trace elements in adults:

Nutrient	Recommended dose	Toxicity/adverse effects
Vitamin A	I mg	Hepatic dysfunction with long term feeding. Effects increased in renal failure
Vitamin D	5 micrograms (200 IU)-Upper limit 2000 IU	

Nutrient	Recommended dose	Toxicity/adverse effects
Vitamin E	15 mg	Antagonist to vitamin A, affect wound healing and platelet dysfunction
Vitamin K	150 micrograms	Do not coadminister with Warfarin.
Vitamin B1 (thiamine)	3 mg	Maximum GI absorption is at 5 mg, excess is excreted in urine
Vitamin B6 (pryridoxine)	1.5 mg/day	>1 gm/day can cause sensory neuropathy and convulsion
Vitamin C	20 mg/day	GI dysfunction, increased uptake of iron promoting bacteria prolification
Folic	400 micrograms/day	Excess can mask the diagnosis of vitamin B12 deficiency leading to neurological complications
Cobalamine (vitamin B12)	2.4 micrograms	
Niacin B3	40 mg per day	Excess doses (treatment of hyperlipidemia) may cause liver toxicity, cutaneous flushing, nausea, vomiting
Zinc	2.4–4 mg/day	G.I symptoms in high doses of 50–150 mg per day
Selenium	20–100 micrograms/day	Brittle hair and nails, fatigue, irritability
Copper	300 to 500 micrograms	In hepatic insufficiency, increase in liver associated enzymes
Manganese	60 to 100 micrograms	Adjust dose with need.

Source: ASPEN, JPEN J Parenter Enteral Nutr 2009 33: 548

Suggested composition of parenteral multivitamin and trace elements products Products for Adults:

Ingredient	Amount Per Ingredient Unit Dose
A (retinol)	Img
D (ergocalciferol or cholecalciferol)	5 micrograms
E (α-tocopherol)	10 mg
K (phylloquinone)	150 micrograms
vitamins C (ascorbic acid)	200 mg
Folic acid	600 micrograms
Niacin	40 mg
B2 (riboflavin)	3.6 mg
B1 (thiamine)	6.0 mg
B6 (pyridoxine)	6.0 mg
B12 (cyanocobalamin)	5 micrograms
Pantothenic acid	15 mg

Ingredient	Amount Per Ingredient Unit Dose
Biotin	60 micrograms
Zinc	2.5 to 5.0 mg
Selenium	20 to 60 micrograms
Copper	0.3 to 0.5 mg
Chromium	10 to 15 micrograms
Manganese	60 to 100 micrograms

Source: ASPEN, JPEN J Parenter Enteral Nutr 2009 33: 548

33.1.2. Enteral Feeds

33.1.2.1. Enteral nutrition background information:

Nutritional adequacy in patients with uncomplicated medical condition can be achieved by a normal nutrient dense meal. However, diseases and other conditions can alter the metabolic and nutritional status of a patients hence warranting the use of a therapeutic diet. A therapeutic diet is modified from a normal diet and is prescribed to meet a medical or special nutritional need. It is part of a clinical treatment and in some cases can be the principle treatment of a condition. It is usually administered under the supervision of a registered dietician/qualified medical staff. Enteral nutrition (EN) is considered when a therapeutic diet from normal diet is not feasible.

EN generally refers to any method of artificial feeding that uses the GIT to deliver part or all of calorie requirements. EN can be commercially prepared or modified using a normal diet. It includes oral nutritional supplements as well as tube feeding via nasogastric, naso-enteral or percutaneous tubes. Enteral formulas can be presented in different forms such as liquid, powder, jellies or diskette.

Thus, EN comprises all forms of nutritional support that imply the use of "dietary foods for special medical purposes. FDA defines medical foods as "a food which is formulated to be consumed or administered enterally under the supervision of a clinician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

EN can be used as a supplemental (nutritionally incomplete) or replacement feeding (nutritionally complete). Nutritional complete formula are formulas that provide 100 percent of the recommend values of carbohydrates, protein, fat, vitamins, and minerals and can be used on its own as a sole source of nutrition. On the other hand, nutritional incomplete formula does not provide the 100% of the recommended values hence used to complement the deficit in a normal diet.

EN is categorized as standard, hydrolyzed and specialized feeds based on molecular form. However, the nutrients should be within recommended values of supplementary/replacement feeds.

Enteral formula classification:

Enteral formula	Form	Characteristics
Polymeric/ standard	Have intact macronutrients in their unaltered state	Contain intact proteins, lipids in form of long-chain triglycerides (LCTs) and carbohydrates as a mixture. Low viscosity 300–500 mosm/kg
Hydrolyzed	Partially hydrolyzed (predigested or semi-elemental) macronutrients) of fully hydrolyzed (elemental	One or more nutrients are hydrolyzed and composition varies.
Specialized formulations	Renal	Whole protein with modified electrolyte content in a caloric dense formula. 2 kcal/mL
	Hepatic	High Branched Chain Amino Acid
	Pulmonary	High % of calories from fat.
	Diabetic	Complex carbohydrate
	Immune enhancing Formulas	Arginine, glutamine, omega-3 fatty acids, antioxidants
	Gluten free	Excludes foods that contain gluten
	Lactose free	Eliminates/restricts a type of sugar-lactose
	Low sodium	sodium less than 2000 mg

EN can also be classified based on composition of the macronutrients:

Classification	Characteristics
Standard (Iso-caloric/normal-caloric)	Similar to average diet. i.e. 1 kcal/mL
High energy high protein	Protein > 15% of total kcal and energy at 1.5–2 kcal/mL
Calorie dense (high energy)	1.5–2 kcal/mL
Fiber containing	0–1.7 g/100 mL in liquid enteral formula 5–15 g/100 g of powdered enteral formula

Indication for use:

Oral nutritional supplements should be considered when nutritional adequacy is <75% of required daily intake.

Tube feeding should be considered when:

- Patients who are not able to tolerate oral feedings within 5 to 7 days.
- For patients whose oral intake is anticipated to be less than 50% of required daily intake for 7–10 days.
- Disorders of digestive system
- Increased nutritional requirements and losses as a result of disease
- Growth failure or chronic malnutrition
- Congenital disorders affecting feeding

Note:

In critically ill patients, tube feeding should be initiated within 48 to 72 hours of admission after fluid resuscitation and when patients are hemodynamically stable.

Complications of EN

- Access Problem: Ulceration, tube displacement, tube Obstruction, leakage from ostomy
- Administration Problems: Aspiration, regurgitation, and microbial contamination
- GI Complications: Constipation, nausea/ vomiting, distention/bloating, delayed gastric emptying, high gastric residuals, diarrhea, hypoalbuminemia malabsorption
- Metabolic Complications: Micronutrient deficiencies, refeeding syndrome, Drug-nutrient interactions, glucose intolerance, hydration issues and electrolyte imbalance

Administration Instruction:

Oral Nutritional Supplements

They are considered when oral dietary intake is <75% of recommended daily intake while monitoring tolerance. Reconstituted formulas should be used within 24hours and any remainder discarded.

Preparation before feeding

- The position of the enteral tube must be confirmed before feed administration.
- The enteral tube should be adequately flushed so as to prevent blockage.
- Position of the patients: should be propped 30–45 degrees to reduce the risks of aspiration.
- Enteral feeds should not be mixed directly with medications
- Nasogastric feeding is for short term use (3 to 4 weeks) while percutaneous endoscopic gastrostomy or jejunostomy is the preferred route for patients requiring tube feedings for more than 4 weeks
- EN should be at room temperature and should not hung for longer than 4 hours for powdered mixtures.

Tube feeding:

The three common methods of tube-feedings administration are bolus feeding, intermittent drip, and continuous drip. Method selection is based on the parent's clinical status and quality of life considerations. One method can serve as a transition to another method as the patient's status changes.

- **Bolus feeding**

  It is applied to patients who are clinically stable with a functional stomach using a syringe pump or gravity. For syringe feeding, administer 5–20 minutes. Maximum dose is 500 mL per feed distributed 3–4 times a day.

- **Intermittent drip feeding**

  It can be given by pump or gravity drip at a frequency of four to six feedings per day

administered for 20 to 60 minutes. Feed administration is initiated at 100 to 150 mL per feeding and increased as tolerated. It should not be used with patients at high risk for pulmonary aspiration.

» **Continuous drip infusion**

It requires a pump and appropriate for patients who do not tolerate large-volume infusions.

The feeding rate is achieved by dividing the total daily volume in millimeters divided by hours in a day usually 18–24hours to give the quantity of feed per hour (milliliters per hour). Feeding is started at one quarter to one half the goal rate and advanced every 8 to 12 hours to the final volume for hyperosmolar feeds (500 to 900 mosm). Feeds with osmolarities between 300 and 500 mOsm/L can be started at full strength.

Fluids

Fluid needs for adults can be estimated at I mL of water per kcal, or 30 to 35 mL/kg of usual body weight for patients without fluid restrictions, undernourished or metabolically unstable patients. Fluids including feeding tube flushes, medications, and IV fluids, should be considered when determining and calculating a patient's intake.

Paediatric

Enteral feeding dosage is based on age, nutritional requirements metabolic status and diseases.

Adopted from: Raju et.al., 2005

In clinically stable children, isotonic formula is started at a rate of 1–2 mL/kg/hour for younger children. The feeding rate is advanced slowly at 0.5–1 mL/kg/hour based on tolerance at every 6–24 hours until the goal volume is achieved. Bolus feeding can be initiated within 24–48 hours if indicated.

In critical illness during acute early phase (1–2 days of admission in critical care unit) aim is to provide 20–30 kcal/kg/day. In acute phase late period (3–7 days) aim is to provide 50–100 kcal/kg/day. Protein requirements during critical illness is 1.5–3 g/kg/day.

Fluid allowance in paediatrics

Notes:

» This calculation does not apply to newborn infants (from 0 to 28 days after full term delivery).

» A maximum volume of 1000 mL of standard formula providing 1 kcal/mL is required for 1-year old child on EN support.

33.1.2.2. Enteral feeds - liquid formulations

These are to be available at LOU 4

Generally available in 500 mL to 1000 mL sizes. Sips are available in 200 mL

High energy protein fat-free hydrolyzed feed

ATC Code: V06D

Liquid, 200 mL, LOU 4

Indications and dose

Can be used by both paediatrics and adults with pancreatic and hepatic disease, malabsorption, short bowel syndrome

Adult

It is dependent on patient's caloric and protein deficit due to inadequate oral food intake.

Paediatric

Individualized based on weight and age

Contraindications:

Not for parenteral use

Not used when there is GI dysfunction

Special warnings and precautions for use

Should be taken in terms of sips over time for better tolerance

Adverse reactions

Bloating, nausea, vomiting and diarrhea.

Nutritionally complete elemental hepatic formula with MCT for oral /Tube feeding

ATC Code: V06D

Liquid, 200 mL, **500 mL,** LOU 4

Indications and dose

For management of adult and paediatric via tube feeding with compromised liver functions and in patients with hyper-catabolic conditions such as burn, sepsis, trauma and burns.

Adult

Should be individualized based on nutritional assessment, branched amino acids requirements and fluid requirements of the patients.

Paediatric

Suitable for paediatric from of age 1 yr- to 12 yrs

Should be individualized based on kcal/body weight/day, protein requirements/body weight/day, branched amino acids requirements and fluid allowance

Contraindications:

Not for parenteral use

Not used when there is GI dysfunction

Special warnings and precautions for use:

Must be used under medical supervision

Continuous drip feeding should be used for better tolerance

Adverse :

Diarrhea and abdominal distention when bolus feeding.

Nutritionally complete glutamine-enriched liquid formula

ATC Code: V06D

Liquid, 500 mL, LOU4

Indications and dose

Prescribed in patients with hyper-catabolism metabolism such as burns and cancer, those with compromised immune functions such as sepsis and HIV-infection

Adult

Should be individualized based on nutritional assessment, fluid requirements and glutamine requirements.

Paediatric

Suitable for paediatric from of age 1 yr to 12 yrs

Should be individualized based on weight and age

Contraindications

Not for parenteral use

Not used when there is GI dysfunction

Adverse effects: Bloating, nausea, dizziness, heartburn and stomach pain

Notes:

- Must be used under medical supervision
- Continuous drip feeding should be used for better tolerance.

Nutritionally complete High energy, high protein oral/tube feed

ATC Code: V06D

Liquid, 200 mL, 500 mL, LOU4

Indications and dose:

For use in the nutritional management of patients with increased energy and protein needs and fluid restricted conditions, e.g., renal insufficiency/impaired kidney function, disease related malnutrition, post total gastrectomy, bowel fistulas, in both adults and children over 1 yr. It can be used as a nutrition supplement or as a total meal replacement.

Adult

Dosage is dependent on nutritional status of the patient, metabolic needs, energy expenditure, and medical condition.

Supplementary nutrition: 400–800 kcal/day

Complete nutrition: 1600–2000 kcal/day

Paediatric

Supplementary and Complete nutrition

Children over 1 year: Based on weight and nutritional needs assessment.

Contraindications

Not suitable whenever EN is not permitted (acute GI bleeding, shock)

Congenital inability to metabolise nutrients in the product.

Not suitable for patients with galactosemia

Not for infants under 1 yr

Special warnings and precautions for use

Not to be given as a bolus feed in EN

Use with caution in children under 6 yrs under medical supervision.

Ensure adequate fluid intake.

Pregnancy and breastfeeding: No known contraindication in pregnant and lactating women.

Adverse effects: Hypersensitivity reactions, Refeeding syndrome.

Nutritionally complete hydrolyzed feeds with MCT fibre-free

ATC Code: V06D

Liquid, 500 mL, LOU4

Indications and dose

For management of adult and paediatric patients with malabsorption/short bowel syndrome, hepatic or pancreatic failure, transition from parenteral nutrition (PN),

when whole protein formulas are not tolerated but enteral is indicated, initial phase after prolonged starvation and in patients with enterocutaneous fistula, Jejunal feeding.

Adult

The dosage should be adapted to the patients' individual requirements and clinical state. It is recommended that it is prescribed as a continuous enteral feeding via gravity set.

Complete nutrition should provide 1500–2000 kcal/day and Protein 1.3 g/kg/day

Paediatric

Based on nutrition, metabolic and medical assessment and needs.

Use with caution in children below 6 years

Contraindications:

Not suitable when EN is not permitted

Not to be used in normal digestive capabilities

Not for parenteral use.

Special warnings and precautions for use: Requires a gravity set for administration or a pump set where a feeding pump is available

Nutritionally complete hypercaloric liquid formula feed

ATC Code: V06D

Liquid, 500 mL, LOU4

Indications and dose

Can be used by both paediatrics and adults with increased catabolism such as in burn, trauma and sepsis patients

Adult

Should be individualized based on patient's nutritional needs.

Paediatric

Suitable for paediatric from of age 1 yr to 12 yrs

Should be individualized based on weight and age.

Contraindications:

Not for parenteral use

Not used when there is GI dysfunction

Special warnings and precautions for use:

Must only be used under medical supervision

Ensure adequate fluid intake

Use with caution in children under 6 years of age

Adverse effects: Bloating, nausea, vomiting and diarrhea when taken in bolus form

Nutritionally complete, hypocaloric oral/tube feed liquid diet with fibre

ATC Code: V06D

Liquid, 200 mL, 500 mL, LOU4

Indications and dose

For use in the dietary management of adult and paediatric patients with hyperglycemia/impaired glucose tolerance, diabetes mellitus, patients with disease related malnutrition or at risk of malnutrition with impaired glucose tolerance, metabolic syndrome, diabetes mellitus, critically ill patients.

Adult

The dosage should be adapted to the patients' individual requirements.

It is recommended that it is prescribed as a continuous/intermittent enteral feed via gravity set.

Complete nutrition should provide 1500–2000 kcal/day.

Paediatric

Based on nutrition, metabolic and medical assessment and needs.

Not suitable for children below 3 years

Used with caution in children between 3 and 6 years

Contraindications:

Not suitable where EN is not permitted

Use with caution in severe organ failure with impaired metabolism

Not suitable for children <3 yrs

Not suitable for patients with galactosemia

Special warnings and precautions for use

Requires a gravity set for administration or a pump set where a feeding pump is available.

Not suitable for patients with galactosemia

Adverse effects: Diarrhea and vomiting, aspiration pneumonia, prolonged use can lead to dysphagia,

Nutritionally complete isocaloric liquid diet with fibre for oral or tube feeding

ATC Code: V06D

Liquid, 200 mL, 500 mL, 1L, LOU4

Indications and dose

Nutritionally complete high protein, high energy sip feed for the nutritional management of disease related malnutrition, anorexia, renal failure, acute and chronic respiratory conditions.

Adult

The dosage should be calculated according to the patients' individual requirements and clinical state. It is recommended that it is prescribed as a sip feed,

Supplemental nutrition, provide 300 to 600 kcal/day and Protein 1.2 to 2 g/kg/day

Paediatric

Based on nutrition, metabolic and medical assessment and needs.

To be used with caution in children below 6 years

Contraindications:

Not suitable when EN is not permitted

Not to be used in normal digestive capabilities

Not for parenteral use.

Nutritionally complete isocaloric liquid diet with fibre-free for oral or tube feeding

ATC Code: V06D

Liquid, 200 mL, 500 mL, 1L, LOU4

Indications and dose

Indicated for EN support in adult and paediatric patients with normal digestive and absorptive capabilities.

Adult

Should be individualized based on nutritional assessment, metabolic needs and the clinical status of the patient.

Paediatric

Suitable for paediatric from of age 1 yr to 12 yrs

Should be individualized based on weight and age

Contraindications:

Not for parenteral use

Not used when there is GI dysfunction

Special warnings and precautions for use

Must be used under medical supervision

Continuous drip feeding should be used for better tolerance.

Rapid infusion may result in nausea, vomiting and or diarrhea. In such cases, administration should be discontinued.

Adverse effects: Diarrhea and abdominal distention if feed administration is in bolus feeding

Nutritionally complete isocaloric paediatric liquid diet for oral or tube feeding

ATC Code: V06D

Liquid, 200 mL, 500 mL, LOU4

Indications and dose

Used in paediatric patients on tube feeding with hyper catabolism such as burns, trauma or sepsis.

Paediatric

Suitable for paediatric from of age 1 yr to 12 yrs

Should be individualized based on weight and age

Contraindications

Not for parenteral use

Not suitable when there is GI dysfunction

Special warnings and precautions for use

Must be used under medical supervision

Continuous drip feeding should be used for better tolerance.

Rapid infusion may result in nausea, vomiting and or diarrhea. In such cases, administration should be discontinued.

Adverse effects: Diarrhea and abdominal distention if feed administration is in bolus feeding.

Nutritionally complete liquid low sodium formula

ATC Code: V06D

Liquid, 500 mL, LOU4

Indications and dose

Suitable for management of both paediatric and adult patients with fluid retention, hypertensive or cardiac failure.

Adult

Should be individualized based on nutritional assessment, sodium and fluid requirements of the patients.

Paediatric

Suitable for paediatric from of age 1 yr to 12 yrs

Should be individualized based on weight and age

Contraindications:

Not for parenteral use

Not used when there is GI dysfunction

Not suitable for infants <6 mths

Adverse effects: Diarrhea and abdominal distention when bolus feeding

Notes:

Must be used under medical supervision

Continuous drip feeding should be used for better tolerance.

A too rapid infusion may result in nausea, vomiting and or diarrhea. In such cases, discontinue the administration.

Nutritionally complete semi-elemental peptide-based formula for oral/tube feed

ATC Code: V06D

Liquid, 200 mL, 500 mL, LOU4

Indications and dose

Can be used by both paediatrics and adults patients with malabsorption, short bowel syndrome and pancreatic failure

Adult

Should be individualized based on patient's nutritional needs.

Paediatric

Suitable for paediatric from of age 1 yr-12 yrs

Should be individualized based on weight and age.

Contraindications

Not for parenteral use

Not suitable for patients with galactosaemia

Special warnings and precautions for use

Must only be used under medical supervision

Ensure adequate fluid intake

Adverse reactions: Bloating, nausea, vomiting and diarrhea

Enteral feeds - powder formulations

Adult nutritionally complete Isocaloric formula

ATC Code: V06D

Powder, 400 g, LOU 4

Indications and dose

Adult

For use in non-disease specific oral and tube feeding

Use as a replacement feed.

For convalesce patients

Dose should be individualized to suit patient's requirements.

Contraindications:

Not intended for use in children unless otherwise instructed by a health care professional.

Not suitable for patients with severe or end stage kidney failure (CKD Stage 4-5), or for patients with Stage 3B CKD who are hyperkalemic or have hyperphosphatemia

Precautions:

Not for IV use.

Not for patients with galactosemia or an intolerance to soya or milk protein.

May not be suitable for patients with poor manual dexterity

Adverse effects: Constipation, nausea, vomiting, diarrhoea.

Interaction with other medicines:

This product may interfere with the absorption of antibiotics. Consult with the nutritionists/dietitians professionals before prescribing.

Notes:

- Use only under medical supervision.
- Suitable as a sole source of nutrition or as a supplement

Adult nutritionally complete elemental peptide formula

ATC Code: V06D

Powder, 20 g – 30 g (sachets), LOU 4

Indications and dose

Adult

For oral and tube feeding

For nutritional management of patients with impaired GI function such as malabsorption/maldigestion, chronic diarrhea, pancreatitis, short bowel syndrome, gut atropy, steatorrhea

Supplemental or sole-source feeding for metabolically stressed patients (e.g., fractures, wounds, burns, surgery, adult pressure ulcers)

GI compromise, e.g., patients with critical illness, e.g., trauma, surgery, GI surgery, protein-energy malnutrition, hypoalbuminaemia, chronic diarrhea, HIV/AIDS, cystic fibrosis, elevated gastric residuals, oncology and radiation enteritis.

It can be used as a full liquid diet or liquid supplement

Dose is individualized to suit patient's requirements

Contraindications:

use with caution in children aged 1–6 years (8–20 kg body weight)

Not suitable for infants under 1 year of age

Not for IV use

Should not be used in patients with known allergy or hypersensitivity to any of its ingredients

Precautions:

Use under medical supervision

Not suitable for children under 10 years of age.

Not suitable for patients with galactosaemia.

Pregnancy or breastfeeding: Dose needs to be modified to suit nutritional needs

Adverse Effects: GI-related intolerance symptoms include nausea, vomiting, diarrhea, constipation, retching, and reflux, bloating and cramps.

Amino Acids and vitamin Granules

ATC Code: V06D

Powder, 5 g - 10 g (sachet), LOU 4

Indications and dose

Adult

Oral and tube feeding for nutritional management of malnutrition

For negative nitrogen balance

Should be individualized to suit patient's requirements

Paediatric

Oral and tube feeding for nutritional management of malnutrition

For negative nitrogen balance

Suitable for child over 6years of age

Individualized to suit patient's requirements

Contraindication: Hypersensitivity to active ingredients, allergic reactions, Hepatic coma, Impaired nitrogen utilization, severe renal failure.

Precautions

Not recommended for patients with phenylketonuria

Not to be used with patients with allergic reaction

Adverse effects. Metabolic imbalances, hyperammonemia, high nitrogen in blood, stupor, coma, aluminum poisoning may occur.

Interaction with other medicines: Not known

High Calorie high protein Formula

ATC Code: V06D

Powder, 200 g, LOU 4

Indications and dose

For oral and tube feeding in adults and paediatrics as a replacement feed

Used for patient with strict fluid restriction

Patients with increased nutritional needs.

For adult and paediatric patients on full liquid diet with dysphagia

Adult

Individualized to suit patient's requirements

Paediatric

Individualized to suit patient's requirements

Precautions:

Should not be used in patients with known allergy or hypersensitivity to any of the ingredients in the product.

Not for use in galactosemia or an intolerance to soya or milk protein.

Not intended for use in children (< 4 years) unless otherwise instructed by a health care professional.

Use with caution in CKD Stage 3 patients with hyperkalaemia – use under guidance of Dietitian in CKD stages 4 and 5.

Not recommended for nutritional management of patient with impaired glucose tolerance.

Adverse effects: Constipation, nausea, vomiting, diarrhoea

Interaction with other medicines: Efficacy may be reduced with patients on ascorbic acid and atorvastatin medication

High Calorie high protein formula

ATC Code: V06D

Powder, 200 g (Diskettes), LOU 4

Indications and dose

For adult and paediatric oral use to relieve hunger in between meals

Suitable for patients with early satiety.

For patients with restricted fluid intake

Can be used to manage hyperemisis in pregnancy

Adult

As per the patients' individual nutritional requirements.

Paediatric: Individualized to suit patient's requirements

Contraindications: Not recommended for body builders

Precautions

Strict adherence to the prescribed dosage to avoid excessive intake.

Not recommended for nutritional management of patients with impaired glucose tolerance.

Adverse effect: Not known

Hepatic formula rich in BCAA

ATC Code: V06D

Powder, 200 g - 500 g, LOU 4

Powder, 50 g (sachet), LOU 4

Indications and dose

Oral and tube feeding for nutritional management of adult and paediatrics patients with liver disease, hepatitis, alcohol induced hepatitis, hepatic encephalopathy, cirrhosis, and nonalcoholic steatotic hepatitis with inadequate per oral intake.

Adult

As per the patients' individual nutritional requirements.

Paediatric: Individualized to suit patient's requirements

Precautions:

Not for use in galactosemia

Not recommended for nutritional management of patient with impaired glucose control

Adverse effects: nausea, vomiting, diarrhoea. Should not be used in patients with known allergy or hypersensitivity to any of the ingredients in the product.

Nutritionally complete low glycemic index formula

ATC Code: V06D

Powder, 50 g (sachet), LOU 4

Indications and dose

Oral and tube feeding for nutritional management of adult and paediatric (>10 years) patients with stress induced hyperglycaemia, diabetes mellitus (Types I and II), impaired glucose tolerance, poor blood glucose control.

Adult

As per the patients' individual nutritional requirements.

Paediatric: Children above 10 years old: Individualized to suit patient's requirements

Precautions:

Not intended for use in children below 4 years unless recommended by a physician or other qualified health care professional.

Not suitable for individuals with galactosemia.

Adverse effect: Abdominal discomfort and/or diarrhea, nausea, vomiting

Notes:

- Need for close monitoring is needed for patient on these products for > 3 months
- Use of high fibre-containing feed should be part of a constipation management plan, including assessment of dietary fibre and fluid intake.

Paediatric nutritionally complete Isocaloric formula

ATC Code: V06D

Powder, 400 g, LOU 4

Indications and dose

Paediatric

Oral and tube feeding for nutritional management of paediatric (6 months to 10 yrs) patients with increased nutritional demands, unable to manage solid foods or recovering from illness.

Dose: As per the patients' individual nutritional requirements.

Precautions:

Not suitable for children with galactosemia.

Do not use a milk substitute

Adverse effect: Nausea, vomiting or abdominal pain.

Notes:

- Not recommended for nutritional management of medical conditions presenting with impaired glucose control and those with severe electrolyte imbalances.

Paediatric Nutritionally complete peptide-based formula

ATC Code: V06D

Powder, 400 g, LOU 4

Indications and dose

Paediatric

Oral and tube feeding for nutritional management of paediatric patients with impaired GI such as Malabsorption/maldigestion, Chronic diarrhea, liver disease, pancreatitis, short bowel syndrome, gut atrophy, steatorrhea, lactose intolerance.

Supplemental or sole source of feeding for metabolically stressed paediatric patients (e.g., with fractures, wounds, burns, pressure ulcers and surgical scars)

Dose: As per the patients' individual nutritional requirements.

Precautions:

Not suitable for children with galactosemia.

Do not use a milk substitute

Not intended for children below 4 years old

Adverse effects: GI-related intolerance symptoms include nausea, vomiting, diarrhea, constipation, retching, and reflux, bloating and cramps. Should not be used in patients with known allergy or hypersensitivity to any of its ingredients.

Specialized Renal Formula

ATC Code: V06D

Powder, 400 g, LOU 4

Indications and dose:

Adult

Oral and tube feeding for nutritional management of adult and paediatric. renal disease on fluid management and with compromised nutritional status.

Dose: As per the patients' individual nutritional requirements.

Precautions:

Do not use as milk substitute

Monitor patient's electrolyte, urea and creatinine levels

Not intended for children below 4 years old.

Adverse effect: GI disturbances, abdominal cramps, Nausea or vomiting

Specialized Semi-elemental peptide formula

ATC Code: V06D

Powder, 400 g, LOU 4

Indications and dose:

Adult

For oral and tube feed or nutritional management of adult and paediatric patients with hepatic and pancreatic failure, GIT disorders, Crohn's disease, critically ill patients with low tolerance to intact protein feeds.

Indicated to preserve and/or restore gut integrity during periods of illness and help prevent the consequences of tube-feeding intolerance

Dose: As per the patients' individual nutritional requirements. The dose or amount of formula varies according to individual nutrient needs as assessed by the dietitian/nutritionist.

Precautions: Not intended for children below 4 years old.

Adverse effects: upset stomach or diarrhea.

33.2. Nutrition Feeds For Managing Severe Acute Malnutrition and Moderate Acute Malnutrition

Sudden reductions in food intake or diet quality combined with pathological causes results in acute malnutrition (hunger related under-nutrition).

Other definitions of malnutrition are protein-energy malnutrition, wasting/Marasmus which happens when the intake of nutrients and energy is too low for a person's needs leading to wasting (loss of body fat and muscle) and do not have bilateral pitting edema and kwashiorkor which results when the child is unable to get enough proteins or essential nutrients hence the child develops edema. Anthropometric cutoffs and various clinical signs are used in grouping malnutrition.

Moderate acute malnutrition (MAM), defined as weight-for-height z-score (WHZ) between –2 and –3 or mid-upper arm circumference (MUAC) between 115 millimeters and <125 millimeters. Treatment at this stage is to correct the existing malnutrition while preventing further deterioration to SAM.

Severe acute malnutrition (SAM), defined as WHZ < –3 or MUAC < 115 millimeters, or the presence of bilateral pitting edema, or both. SAM can present with or without medical complications.

Treatment of Malnutrition

First line treatment for malnutrition is to modify the diet to address any gap in nutrient intake. When this is not possible to achieve, other strategies are used including:

- Use of fortified foods with extra nutrients.
- Use of supplementary feeds to complement normal diet and give extra nutrients. Supplements may be in a form of single or combined nutrients or as feeds enriched with selected nutrients to correct a particular nutrition issue.
- Use of therapeutic feeds used as total replacement feeds in severe cases. A normal healthy diet is introduced slowly as the patient responds to treatment.

Fortified Blended Food (FBF)

distributed in larger quantities as family rations for treating or preventing MAM.

LOU: 2

Type of feed	Indications	Dosage
Fortified blended food (FBF), flour, 415 kcal/100 g (sachet)	For supplementation in children aged 6 months to 9 months	As per criteria in Nutrition and HIV guidelines. Individualized dosage based on nutrition and clinical status may be required in some patients.
Fortified blended food (FBF), flour, 435 kcal/100 g (sachet)	For supplementation in underweight adults and adolescents (age 10 to 17 years) people living with HIV and AIDS/TB adults with body mass index <18.5.	As per criteria in Nutrition and HIV guidelines. Individualized dosage based on nutrition and clinical status may be required in some patients

Type of feed	Indications	Dosage
Fortified Blended Food (FBF), flour, 450 kcal/100 g (sachet)	For supplementation in pregnant women and post-partum mothers with Severe and moderate under-nutrition, slower than average weight gain during pregnancy, showing micronutrient deficiencies or symptoms of disease in HIV/TB patients.	As per criteria in Nutrition and HIV guidelines. Individualized dosage based on nutrition and clinical status may be required in some patients
Fortified Blended Food (FBF), flour, 1,000 kcal/250 g (bag or sachet)	For use in supplementary feeding programmes for children and lactating mothers	As per criteria in Nutrition and HIV guidelines. Individualized dosage based on nutrition and clinical status may be required in some patients

Ready-To-Use Supplementary Food (RUSF)

LOU 2

They are specially formulated bars, pastes, or biscuits that provide high-quality protein, energy, and micronutrients. They are ready to use feeds hence do not require preparation, they typically have very low moisture content and are resistant to microbes.

Type of feed	Indication	Dosage
RUSF, oral paste/bar/ liquid/powder, standard formula (minimum 350 kcal/100 g)	For oral intake for clinical management of inadequate nutrient intake from normal diet due to disease symptoms and/or other related conditions	Based on weight and nutrition needs. Should provide at least 1/3 of required daily allowance for all nutrients.
RUSF, oral paste/ bar/ liquid/powder, standard formula (minimum 510 kcal/100 g)	Management of MAM for children above six months and adults. Used for supplementary purpose in addition to other meals.	Child 6 to 59 months: up-to 1 packet per day. Adults: 2 sachets per day Individualized dosage based on nutrition and clinical status may be required in some patients. Additional water intake is recommended.

Ready-To-Use Therapeutic Food (RUTF)

(LOU 2)

They are designed for the treatment of uncomplicated SAM (No medical complications). They are used as a total meal replacement in severe cases. Family meals are slowly introduced as the patient improves tolerance.

Type of feed	Indications	Dosage
RUTF standard formula (minimum 500 kcal/100 g)	For management of SAM without medical complications in children 6 to 59 months, adolescents, underweight people living with HIV and AIDS and TB who have passed appetite test and can drink liquids.	Children: Depends on weight and age Adults: Up to 4 sachets (2000 kcal) a day based on nutritional status and need. For six to eight weeks. Individualized dosage based on nutrition and clinical status may be required in some patientsAdditional water intake is recommended.

F75 and F100

(LOU 4)

They are specially formulated milks used to treat SAM children below 5 years in the inpatient department. They require preparations and have high moisture content hence cannot be stored for long at room temperature.

Feed	Indications	Dosage
Therapeutic diet feed (F-75), powder for oral liquid, standard formula (400 g tin)	Used in the stabilization phase, during the inpatient management for children 6 to 59 months with SAM. Must be used in inpatient facility under medical supervision.	80 to 100 kcal/ kg/day for 3 to 7 days Start with 2 hourly feeds slowly increasing to 4 hourly feeds over 24 hours based on tolerance. Consider nasogastric feeding if tolerance is below 75% in two consecutive feeds including loses from vomiting.
Therapeutic diet feed (F-100), powder for oral liquid, standard formula (400 g tin)	Used in the growth catch up (rehabilitation) phase, during the inpatient management for children 6–59 months with SAM. Must be used in inpatient facility under medical supervision	Start at 100 kcal/kg/ day during transition and increase gradually to maximum of 200 kcal/kg/day based on tolerance and response to treatment for three to four weeks. RUTF can be introduced in alternate feeds slowly and taken up fully when tolerated.

Adverse effects/precautions/Notes for fortified, supplementary, and therapeutic feeds for management of malnutrition.

- All supplements and therapeutic feeds should be given under the supervision of a qualified health practitioner with consultation from a nutritionist/dietician.
- Prolonged storage can cause rancidity and subsequent off-flavors mainly due to iron and fat.
- There can be risk of toxicity of some nutrients in the fortificants including vitamin A, some B vitamins, folic acid, zinc especially if there is other supplementation other than from the feed. The routine and chronic consumption of large amounts of vitamin A over a period of time can result in a variety of toxic symptoms including liver damage, bone abnormalities and joint pain, alopecia, headaches, vomiting and skin desquamation. Sensory neuropathy has been linked with high intake of B6. Vasodilation

or flushing (i.e. a burning or itching sensation in the face, arms and chest) has been observed as a first adverse effect in patients given high doses of nicotinic acid for the treatment of hyperlipidemia. High folic acid intakes could mask or exacerbate neurological problems, such as pernicious anaemia, in people with low intakes of vitamin B12.

- Based on base ingredients check out for allergic reaction to wheat, soya, milk or nuts.
- Excessive consumption of protein rich supplement may result in ketosis
- Fortified blended foods require cooking before intake while ready to use feeds are taken directly.
- These feeds should not be used as breastmilk substitutes.
- Patients with other medical or physiological conditions might show signs of intolerance including diarrhea, nausea or vomiting.
- Drug nutrient or nutrient –nutrient interactions may be experienced.

34.Radiopharmaceuticals

34.1. Diagnostic Radiopharmaceuticals

34.1.1. Radiopharmaceuticals For Planar and Single Photon Emission Computed Tomography (Spect) Imaging

Technetium-99m Succimer (DMSA)/ Dimercaptosuccinic Acid

ATC code: V09CA02

Injection, prepared from a non-radioactive succimer kit for radiolabeling with 99mTc prior to administration, LOU 6

Indications and dose

Adult

Nuclear imaging evaluation of abnormalities in the renal parenchyma, IV: 74 to 222 MBq (2 to 6 mCi)

Paediatric

Nuclear imaging evaluation of abnormalities in the renal parenchyma, IV: 1.9 to 3.7 MBq/Kg with minimum 11MBq (0.05 to 0.1 mCi)

Contraindications: None known

Precautions: Safety and efficacy in children has not yet been established. Breastfeeding should be suspended for 60 hours after injection for lactating patients. Imaging may need to be delayed for 24 hours post injection in patients with advanced renal failure in whom renal uptake is poor. Care must be taken to avoid unnecessary radiation exposure to patients, staff and members of public.

Adverse effects: Adverse effects are rare. They include syncope, fever, nausea, and maculopapular skin rash.

Technetium-99m Exametazime (HMPAO)/ Hexamethyl Propylene Amine Oxime

ATC code: V09AA01

Injection, prepared from a non-radioactive exametazine kit for radiolabeling with 99mTc prior to administration, LOU 6

Precursor radiopharmaceutical, LOU 6

Indications and dose

Adjunct in SPECT imaging of altered regional cerebral perfusion in stroke, precursor radiopharmaceutical in the preparation of 99mTc-radiolabelled leukocytes: 555 MBq to 1110 MBq (15 mCi to 30 mCi)

Contraindications: None known

Precautions: The cobalt stabilizer vial should be used in the preparation of the cerebral imaging radiopharmaceutical and not in the radiolabeling of leukocytes. All patients should be monitored for hypersensitivity reactions. Cardiopulmonary resuscitation services should be available prior to administration. Care must be taken to avoid unnecessary radiation exposure to patients, staff and members of public.

Adverse effects: Reversible increase in blood pressure, flushing, nausea, malaise, fever, vomiting, fatigue, headache, dizziness, paresthesia and hypersensitivity reactions.

[Iodine-123] Sodium Iodide

ATC code: V09FX02

Oral capsule, 3.7, 7.4, and 14.8 MBq (100, 200, and 400 uCi), LOU 6

Indications and dose

Adult

Evaluation of thyroid function and/or thyroid morphology, oral: 3.7 to 14.8 MBq (100–400 uCi)

Paediatric: Safety and effectiveness in the paediatric population has not been established

Contraindications: None known

Precautions: Care must be taken to avoid unnecessary radiation exposure to patients, members of public and staff. Preparations should not be used 30 hours post calibration.

Adverse effects: Adverse effects are rare. They include nausea, vomiting, chest pain, tachycardia, itching skin, rash and hives.

[Iodine-131] Sodium Iodide

ATC code: V09FX03

Oral capsule, 0.33, 0.61, 1.11, 2.03, and 3.7 MBq (9, 16.5, 30, 55, and 100 µCi/capsule), LOU6

Indications and dose

Adult

Thyroid uptake studies, oral: 0.185 to 0.555 MBq (5 to 15 microcuries)

Scintiscanning, oral: 1.85 to 3.7 MBq (50 to 100 microcuries)

Localization of iodide avid metastatic lesions, oral: 37 MBq (1000 microcuries)

Paediatric: Safety and effectiveness in the paediatric population has not been established

Contraindications: Diagnostic use of sodium iodide I131 is contraindicated in pregnancy

Precautions: Couples of childbearing potential should be counselled on potential fetotoxicity. Use of sodium iodide (I131) should be deferred until the possibility of pregnancy during its usage is ruled out. Care must be taken to avoid unnecessary radiation exposure to patients, members of public and staff.

Adverse effects: Adverse effects with diagnostic application are rare, they include nausea, vomiting, chest pain, tachycardia, itching skin, rash and hives

Technetium-99m Mertiatide (MAG3)/ Mercaptoacetyltriglycine

ATC code: V09CA03

Injection, prepared from a non-radioactive betiatide kit for radiolabeling with 99mTc prior to administration, LOU 5

Indications and dose

Adult

Imaging for diagnosing renal function abnormalities, renal failure, urinary tract obstruction, and renal calculi, IV: 185 MBq (5 mCi) to 370 MBq (10 mCi)

Paediatric

Imaging for diagnosing renal function abnormalities, renal failure, urinary tract obstruction, and renal calculi, IV:

Child over 1 month of age: 2.6 MBq/kg (70 µCi/kg) to 5.2 MBq/kg (140 µCi/kg) with a minimum dose of 37 MBq (1 mCi)

Contraindications: None known

Precautions:

Patients should increase fluid intake and voiding after injection to minimize radiation exposure to the bladder. Care must be taken to avoid unnecessary radiation exposure to patients, staff and members of public.

Breastfeeding:

Suspend until the risk of radiation exposure to breastfeeding children is negligible.

Adverse effects: Nausea, vomiting, wheezing, dyspnea, itching, rash, tachycardia, hypertension, shaking chills, fever, and seizures.

Technetium-99m Medronate (MDP)/ Methylene Diphosphonate

ATC code: V09BA02

Injection, prepared from a non-radioactive medronate kit for radiolabeling with 99mTc prior to administration, LOU 5

Indications and dose

Adult

Skeletal scintigraphy, IV: 740 - 1110 MBq (20 - 30 mCi)

Paediatric

Skeletal scintigraphy, IV:9 - 11 MBq/kg (0.2 - 0.3 mCi/kg)

Contraindications: None known

Precautions: Safety and efficacy in paediatric patients has not been established. Lactating patients should suspend breastfeeding until the risk of radiation exposure to breastfeeding children is negligible. Care must be taken to avoid unnecessary radiation exposure to patients, staff and members of public.

Adverse effects: Adverse effects are rare. They result mainly from hypersensitivity reactions, such as itching, various skin rashes, hypotension, chills, nausea, fever, and vomiting.

Molybdenum-99/Technetium-99m Radionuclide Generator

ATC code: V09FX01

Radionuclide generator, 1, 2, 2.5, 3, 4, 4.5, 5, 6, 7.5, 10, 12.5, 15, 18, 20 Ci of 99Mo, LOU 5

Indications:

As a source of sodium pertechnetate Tc 99m to be used in the preparation of approve 99mTc radiopharmaceuticals

Contraindications: None known

Precautions: Care must be taken to avoid unnecessary radiation exposure to patients, members of the public and staff.

Technetium-99m Sestamibi/Sesta Methoxyisobutylisonitrile

ATC code: V09GA01

Injection, prepared from a non-radioactive sestamibi kit for radiolabeling with 99mTc prior to administration, LOU 5

Indications and dose

Adult

Myocardial perfusion imaging, IV: 370 MBq (rest phase) to 1110 MBq (stress phase) (10 mCi to 30 mCi)

Breast imaging, IV: 740 MBq to 1110 MBq (20 mCi to 30 mCi)

Parathyroid imaging, IV: 740 MBq (20 mCi)

Contraindications: None known

Precautions: Allergic and anaphylactic reactions may occur. Pharmacological induction of myocardial stress may cause adverse effects such as myocardial infarction, hypotension, bronchoconstriction, arrhythmias and cerebrovascular effects. Care must be taken to avoid unnecessary radiation exposure to patients, staff and members of public.

Adverse effects: Commonest adverse effects include parosmia, taste perversion, chest pain, angina, ST segment changes, headache and nausea

Technetium-99m Disofenin (DISIDA)

ATC code: V09DA01

Injection, prepared from a non-radioactive disofenin kit for radiolabeling with 99mTc prior to administration, LOU 6

Indications and dose

Adult

Hepatobiliary imaging for the diagnosis acute cholecystitis or to rule out acute cholecystitis in suspected cases, IV:

Average 70-kg non-jaundiced patient: 37 MBq to 185 MBq (1 mCi to 5 mCi)

Average 70-kg adult patients with serum bilirubin levels greater than 5 mg/dL: 111 MBq to 296 MBq (3 mCi to 8 mCi)

Paediatric: Safety and effectiveness in the paediatric population has not been established

Contraindications: None known

Precautions: Morphine augmentation is needed in cases with patent common duct in whom the gall bladder is not visualizable after 60 minutes of imaging. False positive results may be seen in some causes of cholecystitis such as trauma, TPN, intercurrent disease and nil per oral status. Few patients with cholelithiasis may show false negative scan results. Care must be taken to avoid unnecessary radiation exposure to patients, staff and members of public.

Adverse effects: Adverse effects are rare. They include injection site reactions that may progress to erythema multiforme, chills and nausea.

Technetium-99m Leucocytes

ATC code: V09HA02 (labelled leucocytes)

Injection, LOU 6

Indications and dose

Adult

Adjunct in the localization of intraabdominal infection and inflammatory bowel disease, pulmonary infection, osteomyelitis, IV: 185 MBq to 370 MBq (5 mCi to 10 mCi)

Paediatric

Adjunct in the localization of intraabdominal infection and inflammatory bowel disease, pulmonary infection, osteomyelitis, IV:

Child all ages: 3.7–7.4 MBq/kg (0.1–0.2 mCi/kg).

The usual minimum pediatric administered activity is 18–37 MBq (0.5–1.0 mCi).

The maximum administered activity in a child should not exceed the maximum administered activity for an adult.

Contraindications: None known

Precautions: The cobalt stabilizer vial should be used in the preparation of the cerebral imaging radiopharmaceutical and not in the radiolabeling of leukocytes. The radiolabeled leukocytes should ne administered within one hour of preparation, preferably within 20 minutes. All patients should be monitored for hypersensitivity reactions. Cardiopulmonary resuscitation services should be available prior to administration. Breastfeeding should be suspended, and breast milk expressed and discarded for 12 hours to 24 hours post administration. Pregnant patients should be counselled on the risks of radiation exposure to the fetus or embryo. Care must be taken to avoid unnecessary radiation exposure to patients, staff and members of public.

Adverse effects: Reversible increase in blood pressure, flushing, nausea, malaise, fever, vomiting, fatigue, headache, dizziness, paresthesia and hypersensitivity reactions.

Technetium-99m Mebrofenin (BRIDA)

ATC code: V09DA04

Injection, prepared from a non-radioactive mebrofenin kit for radiolabeling with 99mTc prior to administration, LOU 5

Indications and dose

Adult

Hepatobiliary imaging, IV:

Average 70-kg non-jaundiced patient: 74–185 MBq (2–5 mCi)

Average 70-kg adult patients with serum bilirubin levels greater than 1.5 mg/dL: 111–370 MBq (3–10 mCi)

Paediatric: Safety and effectiveness in the children below 18 years of age has not been established

Contraindications: Known hypersensitivity to mebrofenin

Precautions: Effectiveness and safety of this preparation in patients of age less than 18 years have not been established. In lactating patients, feeds alternative to patient's milk should be instituted.

Adverse effects: Adverse effects are rare. They include urticaria, rash, chills and nausea.

Technetium-99m Pentetate (DTPA)

ATC code: V09CA01 and V09EA01

Injection, Inhalation, prepared from a non-radioactive pentetate kit for radiolabeling with 99mTc prior to administration, LOU 6

Indications and dose

Adult

Brain imaging: 370 to 740 MBq (10 to 20 mCi)

Renal visualization and perfusion assessment: 370 to 740 MBq (10 to 20 mCi)

Renal visualization and assessment of glomerular filtration rate: 111 to 185 MBq (3 to 5 mCi)

Estimation of glomerular filtration rate without renal imaging: 7.4 to 18.5 MBq (0.2 to 0.5 mCi)

Lung ventilation studies (in the nebulizer), aerosol inhalation: 925 to 1850 MBq (25 to 50 mCi) to achieve a lung dose of approximately 18.5 to 37mBq (0.5 to 1mCi)

Paediatric

Renal visualization and perfusion assessment: 3.7 to 7.4MBq/kg (0.1 to 0.2mCi/kg) Maximum 37 to 185 MBq (1 mCi to 5 mCi)

Estimation of glomerular filtration rate without renal imaging: 7.4 to 18.5 MBq (0.2 to 0.5 mCi)

Lung ventilation scan (in the nebulizer), aerosol inhalation: 925 MBq (25 mCi) to achieve a lung dose of approximately 18.5 mBq (0.5 mCi)

Contraindications: Hypersensitivity to any of the components of the preparation

Precautions: Inhalation of the preparation may cause bronchospasms. Hypersensitivity reactions including anaphylaxis may occur. Care must be taken to avoid unnecessary radiation exposure to patients, staff and members of public.

Adverse effects: Allergic reactions

[Technetium-99m] Sodium Pertechnetate

ATC code: V09FX01

Injection, eluted from approved 99Mo/99mTc radionuclide generator, LOU 6

Precursor radiopharmaceutical, eluted from approved 99Mo/99mTc radionuclide generator, LOU 5

Indications and dose

Adult

Vesico-ureteral imaging, IV: 18.5 to 37 MBq (0.5 to 1 mCi)

Thyroid gland imaging, IV: 37 to 370 MBq (1 to 10 mCi)

Salivary gland imaging, IV: 37 to 185 MBq (1 to 5 mCi)

Nasolacrimal drainage imaging, IV: Maximum 3.7 MBq (100µCi)

Paediatric

Vesico-ureteral imaging, IV: 18.5 to 37 MBq (0.5 to 1 mCi)

Thyroid gland imaging, IV: 2.22 to 2.96 MBq (60 to 80 µCi)/kg body weight

Contraindications: None known

Precautions: Breastfeeding babies of lactating patients should be offered alternative feeds after injection until the risk of radiation exposure to the breastfeeding baby is negligible. Care must be taken to avoid unnecessary radiation exposure to patients, staff and members of public.

Adverse effects: Adverse effects are rare. They include allergic reactions.

34.1.2. Radiopharmaceuticals For Positron Emission Tomography (PET) Imaging

[Fluorine-18] Prostate Specific Membrane Antigen (PSMA) 1007

ATC Code: *N/A*

Injection, 0.74 – 2.7 GBq/mL (20 – 100 mCi/mL), LoU 6

Indications and dose

Adult

Assessment of overexpression of PSMA (prostate specific membrane antigen) to assist in the evaluation of the malignancy in patients with an existing diagnosis of prostate cancer, 3 – 5 MBq/Kg

Contraindications: *Hypersensitivity to any ingredient of the product*

Precautions: *Care must be taken to avoid unnecessary radiation exposure to patients, staff and members of public.*

Adverse effects: *None known*

[Fluorine-18] Fluorodeoxyglucose (FDG)

ATC code: V09IX04

Injection, 0.74 – 11.1 GBq (20 – 300 mCi/mL), LOU 5

Indications and dose

Adult

Oncology: For assessing abnormal glucose metabolism to assist in evaluating malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer

Cardiology: For identifying left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging

Neurology: For identifying regions of abnormal glucose metabolism associated with foci of epileptic seizures

In all indicated clinical settings, IV: 5–10 mCi (185–370 MBq)

Paediatric

Neurology, IV: 2.6 mCi

Contraindications: None

Precautions: Suboptimal image quality may be seen for cases of uncontrolled blood glucose levels. Ensure two days of normoglycemia prior to fluorodeoxyglucose f18 injection. Like with all radiopharmaceuticals, fluorodeoxyglucose f18 increases the cumulative radiation dose to the patient. Fluorodeoxyglucose f18 should be handled in a way that avoids unnecessary radiation exposure to patient's, members of the public and health care workers.

Adverse effects: Adverse effect are rare. They include Hypersensitivity reactions with pruritus, edema and rash.

Gallium-68 Oxodotreotide (DOTATATE)

ATC code: V09IX09

Injection, 40 micrograms of oxodotreotide kit for radiolabeling with up to 1110 MBq (30 mCi) of [68Ga]GaCl2, LOU 6

Indications and dose

Adult

Positron emission tomography for localization of somatostatin receptor-positive neuroendocrine tumors, IV: 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4 mCi)

Paediatric:

Follow adult dosing

Contraindications: None

Precautions: Image interpretation errors may occur as gallium oxodotreotide Ga 68 uptake is also seen in non-malignant conditions. It should be used in a way that avoids unnecessary radiation exposure to patients, members of public and health care workers.

Adverse effects: No known serious adverse effects

Germanium-68/Gallium-68 Radionuclide Generator

ATC code: V09X

Radionuclide generator, 0.74 – 1.85 GBq, LOU 6

Indications:

Elution of gallium (68Ga) chloride solution for radiolabelling-approved gallium 68 radiopharmaceuticals

Contraindications: Gallium (68Ga) chloride solution should not be injected into patients

Precautions: The radionuclide generator should be used in a way that avoids unnecessary radiation exposure to patients, members of public and health care workers.

34.2. Therapeutic Radiopharmaceuticals

[Iodine-131] Sodium Iodide

ATC code: V10XA01

Oral solution, 5 mCi/mL, 25 mCi/mL, LOU 6

Indications and dose

Adult

Hyperthyroidism, oral: 148 to 370 MBq (4 to 10 mCi); toxic nodular goitre and other situations may require larger doses

Thyroid carcinoma, oral: 3700 to 5550 MBq (100 to 150 mCi)

Radioiodine post-operative ablation of residual thyroid tissue, oral: 1850 MBq (50 mCi)

Paediatric

Safety and effectiveness in the paediatric population has not been established

Contraindications: Therapeutic use of sodium iodide I131 is contraindicated in pregnancy, patients with vomiting and diarrhea, iodide non-avid malignancies such as majority of medullary and anaplastic carcinomas.

Precautions: Couples of childbearing potential should be counselled on potential fetotoxicity. Use of sodium iodide I131 should be deferred until the possibility of pregnancy during its usage is ruled out. Care must be taken to avoid unnecessary radiation exposure to patients, members of the public and staff.

Adverse effects: Common adverse effects with therapeutic application are radiation induced thyroiditis, thyroid enlargement, elevated thyroid stimulating hormone levels, hypersensitivity reactions, radiation toxicity, transient infertility and radiation exposure to other members of the public.

Lutetium-177 Oxodotreotide (Dotatate)

ATC code: V10XX04

Injection, 370 MBq/mL (10 mCi/mL), LOU 6

Indications and dose

Adult

Neuroendocrine somatostatin-positive gastroenteropancreatic tumors: 7.4 GBq (200 mCi) every 8 weeks to total of 4 doses

Paediatric

Safety and effectiveness in the paediatric population has not been established

Contraindications: None known

Precautions: Patients should be monitored for signs of myelosuppression, nephrotoxicity, hepatotoxicity and neuroendocrine crisis. Withholding, reducing the dose or discontinuing therapy should be informed by severity of toxicity. Patients of childbearing potential should be counselled on its fetotoxicity potential and offered effective contraception methods. It may also cause infertility. Care must be taken to avoid unnecessary radiation exposure to patients, members of the public and staff.

Adverse effects: Lymphopenia, increased gamma-glutamyl transferase, vomiting, nausea, increased AST, increased ALT, hyperglycemia and hypokalemia.

35. Medicines For Benign Prostatic Hyperplasia (BPH)

Finasteride

ATC code: G04CB01

Tablet, 5 mg, LOU 4

Indications and dose

Adult

Benign prostatic hyperplasia, oral: 5 mg daily, review treatment at 3–6 months and

then every 6–12 months (may require several months treatment before benefit is obtained). Used in combination with tamsulosin

Contraindications: Hypersensitivity. Women of childbearing potential, children, and adolescents

Precautions: Use with caution with obstructive uropathy, carefully monitor patients with large residual urinary volume or severely diminished urinary flow. Use caution in liver disease. May cause decreased serum PSA in presence of prostate cancer, increases in PSA levels from nadir while on finasteride may signal the presence of prostate cancer and should be carefully evaluated (even if PSA value within normal range).

Pregnant and potentially pregnant women: should not handle crushed or broken tablets or semen of male partner, may have negative impact in foetal development

Adverse effects: hypersensitivity reactions, angioedema, palpitation, sexual dysfunction, increased hepatic enzymes.

Tamsulosin

ATC code: G04CA02

Capsule, 400 micrograms (as HCl), LOU 4

Indications and dose

Adult

Benign prostatic hyperplasia, oral: One capsule daily, to be taken after breakfast or the first meal of the day

Contraindications: Hypersensitivity

Precautions: Use with caution in coronary artery disease, liver disease, general anesthesia. Orthostatic hypotension may occur. Priapism rarely reported. Prostatic cancer should be ruled out before therapy is initiated. May cause syncope (first-dose effect). Discontinue if angina symptoms occur or worsen. Intraoperative floppy iris syndrome has been reported in patients receiving alpha1 blockers at time of cataract surgery, association is unclear. Patients with sulfa allergy have rarely developed allergic reaction, avoid use if previous sulfa allergy reactions have been life-threatening. Not for use as antihypertensive drug. May exacerbate heart failure

Adverse effects: Dizziness, headache, palpitation, rhinitis, orthostatic hypotension, GI disorders, hypersensitivity reactions.

Interactions with other medicines:

- Drugs that increase concentration of tamsulosin:
  - Antifungals: ketoconazole, fluconazole
  - Macrolides. Avoid or adjust dose
  - CCBs: diltiazem, verapamil
  - Protease inhibitors
- Drugs that decrease concentration of tamsulosin:
  - Anti-epileptics (phenobarbitone, carbamazepine, phenytoin)
  - Rifampicin
  - Increased risk of hypotension when given with other hypotensive drugs

Notes: The capsule must be swallowed whole and should not be crunched or chewed as this interferes with the modified release of the active ingredients

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Appendix 1: Formulary Amendment Proposal Form

Kenya National Medicines Formulary Amendment Proposal Form

Complete each of the sections and submit the form together with the hard and/or soft copies of supporting evidence and any other relevant documentation to:

The Head, Health Products and Technologies
Ministry of Health
Afya House, Cathedral Road
Box 30016-00100, Nairobi, Kenya
Email: pharmacyhpt@health.go.ke
pharmacyhpt2019@gmail.com

Name of Proposer: _____

Designation: _____

Workplace: _____

Contact: _____

Tel: _____ Email: _____

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1. **Details to be amended** (Please tick)
   a. Classification of medicine [ ]
   b. Section/Subsection titles [ ]
   c. Anatomical Therapeutic Chemical (ATC) code [ ]
   d. Formulation [ ]
   e. Level of Use [ ]
   f. Indications and dose [ ]
   g. Contraindications [ ]
   h. Precautions [ ]
   i. Adverse effects [ ]
   j. Interactions with other medicines [ ]
   k. Special Notes [ ]
2. **Type of amendment proposed** (*please tick*)
   a. Addition [ ]
   b. Deletion [ ]
   c. Other [ ]
3. **Details of proposal:**
4. **Supporting arguments/evidence base:**
5. **Supporting references/relevant documentation:**

Signature: _____ **Date:** _____

Appendix 2: List of Contributors

The following is a list of those who contributed to the various stages of KNMF 2023 development indicating their institutional or professional affiliation.

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Appendix 3: Replacement of Fluids & Electrolytes In Children With Acute Diarrhoea

WHO Recommends Plans A, B and C, below.

Plan A: no dehydration

Nutritional advice, increased fluid intake (e.g., unsalted soup, unsalted rice water, yoghurt, or plain water), at least one fluid that normally contains salt (e.g., ORS solution, salted drinks including salted rice water and vegetable or chicken soup with salt) and zinc supplementation at home are usually sufficient.

The aim is to give as much nutrient-rich food as the child will accept.

Breastfeeding should always be continued to reduce the risk of diminishing supply.

The child should be given as much fluid as the child wants until diarrhoea stops and, as a guide, after each loose stool the following should be used:

Child under 2 years 50–100 ml (a quarter to half a large cup) of fluid,

2–10 years 100–200 ml (a half to one large cup),

older than 10 years as much fluid as the child can take.

Parents should be advised about circumstances in which they should seek further advice.

Plan B: moderate dehydration

Whatever the child's age, a 4 hour treatment plan is applied to avoid short-term problems. Parents should be shown how to give approximately 75 mL/kg of oral rehydration solution over a 4 hour period, parents should be watched to see how they cope at the beginning of the treatment.

A larger amount of solution (up to 20 mL/kg/hour and maximum 750 mL/hour) can be given if the child continues to have frequent stools or if the child wants more than the estimated amount of ORS solution, and there are no signs of overhydration (e.g., oedematous eyelids).

In case of vomiting, rehydration must be discontinued for 10 minutes and then resumed at a slower rate.

In younger children, breastfeeding should be continued on demand and the mother should be encouraged to do so. Older children should receive milk and nutritious food as normal after completing the 4 hours of oral rehydration. The child's status must be reassessed after 4 hours to decide on the most appropriate subsequent treatment.

If signs of dehydration worsen, and if the child develops signs of severe dehydration, IV rehydration should be started as per treatment plan C. Zinc supplementation should begin as soon as the child can eat and has completed 4 hours of rehydration.

Oral rehydration solution should continue to be offered once dehydration has been controlled, for as long as the child continues to have diarrhoea.

Plan C: severe dehydration

Hospitalization is necessary, but the most urgent priority is to start rehydration. The preferred treatment for children with severe dehydration is rapid IV rehydration. In hospital (or elsewhere), if the child can drink, oral rehydration solution (20 mL/kg/hour) should be given before the IV rehydration, then 5 mL/kg/hour during the IV rehydration).

For IV rehydration, it is recommended that compound solution of sodium lactate (or, if this is unavailable, sodium chloride 0.9% IV infusion) is administered at a rate adapted to the child's age.

IV rehydration using compound sodium lactate solution or sodium chloride 0.9% infusion

Infant: 30 mL/kg over 1 hour, then 14 mL/kg/hour for 5 hours.

Child: 30 mL/kg over 30 minutes, then 28 mL/kg/hour for 2.5 hours.

If the IV route is unavailable, a nasogastric tube is also suitable for administering oral rehydration solution.

Nasogastric rehydration using oral rehydration solution

Infant or **Child:** 20 mL/kg/hour for 6 hours (total 120 mL/kg).

If the child vomits, the rate of administration of the oral solution should be reduced. The child's status reassessed after 3 hours (6 hours for infants) and treatment continued as appropriate with plan A, B or C.

Appendix 4: AWaRe Classification of Antibiotics

Access Group	KEML 2023 Access group antibacterials
This group includes antibiotics and antibiotic classes that have activity against a wide range of commonly encountered susceptible pathogens while showing lower resistance potential than antibiotics in Watch and Reserve groups. Access antibiotics should be widely available, affordable and quality-assured to improve access and promote appropriate use. Selected Access group antibiotics are included on the WHO EML as essential first-choice or second-choice empirical treatment options for specific infectious syndromes.	Amikacin Amoxicillin Amoxicillin + Clavulanic acid Ampicillin Benzathine Benzylpenicillin Benzylpenicillin Cefalexin Cefazolin Cefixime Doxycycline Flucloxacillin Gentamicin Metronidazole Nitrofurantoin Phenoxymethylpenicillin (Penicillin V) Tinidazole
Watch Group	**KEML 2023 Watch group antibacterials**
This group includes antibiotics and antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the critically important antimicrobials for human medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. Watch group antibiotics should be prioritized as key targets of national and local stewardship programmes and monitoring. Selected Watch group antibiotics are included on the WHO EML as essential first-choice or second-choice empirical treatment options for a limited number of specific infectious syndromes.	Azithromycin Cefixime Cefotaxime Ceftazidime Ceftriaxone Cefuroxime Ciprofloxacin Clarithromycin Clindamycin Co-trimoxazole (Sulfamethoxazole + Trimethoprim) Erythromycin Piperacillin + Tazobactam

Reserve Group	KEML 2023 Reserve group antibacterials
This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multidrug-resistant organisms and treated as "last-resort" options. Their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. They could be protected and prioritized as key targets of national and international stewardship programmes, involving monitoring and utilization reporting, to preserve their effectiveness. Selected Reserve group antibiotics (shown here) are included on the WHO EML when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably Carbapenem-resistant Enterobacteriaceae.	Ceftazidime + Avibactam Colistin Fosfomycin Linezolid Meropenem Polymyxin B Teicoplanin Tigecycline Vancomycin

Source: The above table has been adapted from the 2019 National Antimicrobial Stewardship: Guidelines for Health care settings.

WHO recommends that each country adapt the antibiotic medicines listed as Access, Watch or Reserve to its settings.

AWaRe classification as listed here is as per KEML 2019; 7.2 Antibacterials; Page 39 to 47

Index

B

C

D

E

F

G

H

I

N

O

P

T

USAID MEDICINES, TECHNOLOGIES AND
PHARMACEUTICAL SERVICES (MTaPS) PROGRAM
Improved Access. Improved Services. Better Health Outcomes.