



**Ministry of Public Health
General Directorate of Pharmacy Affairs
Avicenna Pharmaceutical Institute**



**AFGHANISTAN NATIONAL
FORMULARY
ESSENTIAL MEDICINES**

January 2015

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About SPS

The Strengthening Pharmaceutical Systems (SPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to the most efficacious, safe and cost-effective medicines and appropriate use of medicines.

Acknowledgments

A medicine formulary is an important tool for ensuring appropriate and effective use of medicines in health system service delivery. Afghanistan has the experience of using a medicine formulary since the first edition, published decades ago, through the seventh edition, published in 2007. Those editions concerned the Licensed Medicines List of Afghanistan.

This eighth edition of the Afghanistan National Formulary specifically focuses on the latest Essential Medicines List of Afghanistan and is based on the National Standard Treatment Guidelines for Primary Level, which was launched in 2015. It is a drug information manual relevant to the Basic Package of Health Services (BPHS) and the Essential Package of Hospital Services (EPHS), and its aim is to facilitate the effective use of medicines in the public sector by health staff at primary-level health facilities.

To develop the formulary, a National Formulary Committee was established and representatives from relevant institutions and professional academia were assigned, including members of Kabul Medical University, Faculty of Pharmacy; professional doctors and pharmacists associations; the World Health Organization; and the Strengthening Pharmaceutical Systems Project. The committee operated under the authority of the Ibn Sina Pharmacy Institute, the Pharmacy Affairs General Directorate, and the National Drug and Therapeutic Committee of Ministry of Public Health.

The Afghanistan National Formulary Committee successfully developed the National Formulary for Essential Medicines through a regular and systematic process and with the contribution of experienced pharmacists and medical doctors, as planned. As a second step, the general version of the National Formulary for Licensed Medicines of Afghanistan is under development and will soon be completed.

The Ministry of Public Health congratulates the Afghanistan National Formulary Committee, editors, proofreaders, and all stakeholders who have contributed their services and acknowledges their commitment to this process, and wishes all the members success in the development of the Afghanistan National Formulary for Licensed Medicines List (LML). The Ministry of Public Health would also like to thank the organizations that have made available their representatives to actively participate and support this national process.

Special thanks go to the Strengthening Pharmaceutical Systems Project, funded by US Agency for International Development (USAID), which made possible the revision process of the Afghanistan National Formulary for Essential Medicines.

With regards,

Dr. Ferozuddin Feroz,

Minister of Public Health of Afghanistan

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Preface

The National Formulary of Afghanistan is a reference and guide for physicians, pharmacists, and other health staff who provide health services in the country. With the latest developments in medical and pharmaceutical sciences and the availability of thousands of medicines in the market, it is not possible for health care staff to memorize all necessary information. Therefore it is the responsibility of each country's professionals in medicine and pharmacy to share scientific information with health care staff to ensure the rational use of these medicines. The objective of this document—known as “the formulary”—is to provide accurate, scientific, and unbiased information about the essential medicines used in the country. Since global medical research continuously evolves, it is good practice to update and revise the formulary regularly.

Several decades have passed since the publication of the first official Afghanistan Formulary. The first formulary only contained the names of medicines and information was very brief. The Afghan National Formulary, sixth edition, was published in 1996 containing important information about the essential medicines. The seventh edition of the formulary (2007) focuses more on information related to the licensed medicines in the country.

The development of this eighth edition, the Afghanistan National formulary for Essential Medicines, has been recommended by the National Drug and Therapeutics Committee and approved by the Ministry of Public Health (MoPH). An Afghanistan National Formulary Committee was created, encompassing professionals, lecturers, contributors from scientific and academic resources, and health services providers, all under the umbrella of the Ibn Sina Pharmacy Institute. In addition, a number of elite pharmacists volunteered to prepare the first draft of this national formulary for essential medicines. Drafts were reviewed by one lecturer and then presented to the National Formulary Committee for approval. During the process, the WHO Model Formulary 2008, the British National Formulary 2014, and Martindale 2009 were primary references, as well the MoPH national program guidelines. When needed, other resources from academic institutions and Internet sites were used.

During this revision of the formulary, several steps recommended by WHO were systematically considered and all medicines included in the revised 2014 National Essential Medicines List of Afghanistan, with relevant information, were categorized based on WHO classification. Efforts were also made to eliminate unnecessary information.

For each medicine, the following information is included: dosage form, indications, contraindications, cautions, drug interactions, dose, and adverse effects. All medicines in this formulary version are based on the Essential Medicines List of Afghanistan; it also includes the strengths that are included in the Licensed Medicines List of Afghanistan (specifically marked in italic and with an asterix). At the end of the manual are annexes related to important information concerning interactions; use in pregnancy, use in breast-feeding, use in renal and hepatic impairment; a table of antidotes; and a reporting form for adverse drug reactions (ADRs).

For medicines containing more than one active ingredient, it is recommended to refer to the information related to each active ingredient separately. In some paragraphs where general information is provided, a few of the medicines mentioned are not included in the official Licensed Medicine List of Afghanistan; the purpose here is only to share general information, not to promote their prescription.

Despite all efforts, it is possible that certain errors have been overlooked, and the authors would be grateful to have any such error or incompleteness reported. Although we hope that the National Formulary of Essential Medicines 2015 will be a useful guide to many prescribers and dispensers, it is important to remember that, when in doubt, it remains the responsibility of the prescribing medical professional to ensure that the active substances and doses prescribed and dispensed correspond with the therapeutic need of the patient and conform to the manufacturer's specifications. Please send any identified errors or other comments that may help improve future versions of this manual to API/GDPA at the following addresses:

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With regards,

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Abbreviations and acronyms

ACE	angiotensin-converting enzyme
ACTH	adrenocorticotrophic hormone
ADR	adrenocorticotrophic hormone
AIDS	acquired immunodeficiency syndrome
APD	automated peritoneal dialysis
API	Avicenna Pharmaceutical Institute
ART	antiretroviral therapy
AV	atrioventricular
BCG	bacillus Calmette–Guérin
BPHS	Basic Package of Health Services
BUN	blood urea nitrogen
CAPD	continuous ambulatory peritoneal dialysis
CNS	central nervous system
CSF	cerebrospinal fluid
DMARD	disease-modifying anti-rheumatic drug
DOT	directly observed therapy
DPT	diphtheria-pertussis-tetanus vaccine
ECG	electrocardiogram
ECT	electroconvulsive therapy
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EML	Essential Medicines List
ENL	erythema nodosum leprosum
EPHS	Essential Package of Hospital Services
EPI	Expanded Programme on Immunization
g	gram
G6PD	glucose-6-phosphate dehydrogenase deficiency
GDPA	General Directorate of Pharmaceutical Affairs
GFR	glomerular filtration rate

HbsAg	hepatitis B virus surface antigen
HepB	hepatitis B vaccine
Hib	<i>Haemophilus influenza</i> type B vaccine
HIV	human immunodeficiency virus
HPA	hypothalamo-pituitary-adrenal
ICU	intensive care unit
IM	intramuscular
inj	injection
INR	international normalized ratio
ISO	International Organization for Standardization
IU	international units
IUD	intrauterine contraceptive device
IV	intravenous
kg	kilogram
L	liter
LML	Licensed Medicines List
MAOI	monoamine oxidase inhibitor
max.	maximum
MB	multibacillary
mcg	microgram
MDR	multidrug-resistant
MDT	multidrug therapy
mg	multidrug therapy
min	minute
ml	milliliter
mmol	millimole
MMR	measles, mumps, and rubella vaccine
MoPH	Ministry of Public Health
MR	measles and rubella vaccine

MRSA	methicillan-resistant <i>Staphylococcus aureas</i> infection
MSH	Management Sciences for Health
MU	million units
NSAIM	non-steroidal anti-inflammatory medicine
ORS	oral rehydration salts
PB	paucibacillary
PCV	pentavalent conjugate vaccine
PCV-7	7-valent conjugate vaccine
PPD	purified protein derivative
PTB	pulmonary tuberculosis
ReSoMal	rehydration salts for malnourished child
Rh	Rh factor
SPS	Strengthening Pharmaceutical Systems
SSRI	selective serotonin-reuptake inhibitor
STG	standard treatment guideline
TB	tuberculosis
USAID	US Agency for International Development
VAPP	vaccine associated paralytic polio
WHO	World Health Organization

GENERAL INFORMATION FOR PRESCRIBERS AND DISPENSERS

RATIONAL APPROACH TO THERAPEUTICS

Drugs should only be prescribed when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risks involved. Bad prescribing habits lead to ineffective and unsafe treatment, exacerbation or prolongation of illness, distress and harm to the patient, and higher costs.

The following steps will help to remind prescribers of the rational approach to therapeutics:

1. Define the patient's problem

Whenever possible, making the right diagnosis is based on the integration of many pieces of information: the complaint as described by the patient; a detailed history; physical examination; laboratory tests; and X-rays and other investigations. This will help in rational prescribing, always bearing in mind that diseases are evolutionary processes.

2. Specify the therapeutic objective

Doctors must clearly state their therapeutic objectives based on the pathophysiology underlying the clinical situation. Very often, physicians must select more than one therapeutic goal for each patient.

3. Select the therapeutic strategies

The selected strategy should be agreed upon with the patient; this agreement on outcome, and how it may be achieved, is termed *concordance*. The selected treatment can be non-pharmacological and/or pharmacological; it also needs to take into account the total cost of all therapeutic options.

a. Non-pharmacological treatment

It is very important to bear in mind that the patient does not always need a drug to treat their condition. Very often, health problems can be resolved by a change in lifestyle or diet, use of physiotherapy or exercise, provision of adequate psychological support, and other non-pharmacological treatments; these have the same importance as a prescription drug, and instructions for such treatments must be written, explained, and monitored in the same way.

b. Pharmacological treatment

i. Selecting the correct group of drugs

Knowledge of the pathophysiology involved in the clinical situation of each patient and knowledge of the pharmacodynamics of the chosen group of drugs are the two fundamental principles underlying rational therapeutics.

ii. Selecting the drug from the chosen group

The selection process must consider benefit/risk/cost information. This step is based on evidence about the maximal clinical benefits of the drug for a given indication (efficacy) with the minimum production of adverse effects (safety). It must be remembered that each drug has adverse effects; it is estimated that up to 10% of hospital admissions in industrialized countries are due to adverse effects. Not all drug-induced injury can be prevented, but much of it is caused by inappropriate selection of drugs. In cost comparisons between drugs, the cost of the total treatment and not only the unit cost of the drug must be considered.

iii. Verifying the suitability of the chosen pharmaceutical treatment for each patient

The prescriber must check whether the active substance chosen, its dosage form, standard dosage schedule, and standard duration of treatment are suitable for each patient. Drug treatment should be individualized to the needs of each patient.

iv. Prescription writing

Because the prescription is the link between the prescriber, the pharmacist (or dispenser), and the patient, it is vital to the successful management of the presenting medical condition. This item is covered in more detail in a following section (see Prescription writing).

v. Giving information, instructions, and warnings

This step is important to ensure patient adherence and is covered in detail in a following section (see Adherence [compliance] with drug treatment).

vi. Monitoring treatment

Evaluation of the follow-up and the outcome of the treatment allow it to be discontinued (if the patient's problem is resolved) or its reformulation when necessary. This step provides important information about the effects of drugs, contributing to the body of knowledge of pharmacovigilance, which is needed to promote the rational use of drugs.

VARIATION IN DOSE-RESPONSE

Success in drug treatment depends not only on the correct choice of drug but also on the correct dose regimen. Unfortunately, drug treatment frequently fails because the dose is too small or produces adverse effects because it is too large. This is because most texts, teachers, and other drug information sources continue to recommend standard doses.

The concept of a standard or “average” adult dose for every medicine is firmly rooted in the mind of most prescribers. After the initial “dose ranging” studies on new drugs, manufacturers recommend a dosage that appears to produce the desired response in the majority of subjects. These studies are usually done on healthy, young male Caucasian volunteers, rather than on older men and women with illnesses and of different ethnic and environmental backgrounds. The use of standard doses in the marketing literature suggests that standard responses are the rule, but in reality there is considerable variation in drug response. There are many reasons for this variation, which include adherence (see below), drug formulation, body weight and age, composition, variation in drug absorption, distribution, metabolism, and excretion, variation in pharmacodynamics, disease variables, and genetic and environmental variables.

Drug formulation

Poorly formulated drugs may fail to disintegrate or dissolve. Enteric-coated drugs have been known to pass through the gastrointestinal tract intact. In drugs with a narrow therapeutic-toxic ratio, changes in absorption can produce sudden changes in drug concentration. For such drugs, quality control surveillance should be carried out.

Body weight and age

Although the concept of varying the dose with the body weight or age of children has a long tradition, adult doses have been assumed to be the same irrespective of the patient’s size or shape. Yet adult weights vary two- to threefold, while a patient with a large fat mass can store large excesses of highly lipid-soluble drugs compared with a lean patient of the same weight.

Age changes can also be important. Adolescents may oxidize some drugs relatively more rapidly than adults, while the elderly may have reduced renal function and eliminate some drugs more slowly.

Dose calculation in children

Children's doses may be calculated from adult doses by using age, body weight, or body surface area, or by a combination of these factors. The most reliable methods are those based on body surface area. Body weight may be used to calculate doses expressed in mg/kg.

Young children may require a higher dose per kilogram than adults because of their higher metabolic rates. Other problems need to be considered. For example, calculation by body weight in an overweight child may result in the administration of much higher doses than necessary; in such cases, dose should be calculated from an ideal weight, related to height and age. Nomograms can be used to calculate body surface values based on a child's height and weight. Where the dose for children is not readily available, prescribers should seek specialist advice before prescribing for a child.

PHYSIOLOGICAL AND PHARMACOKINETIC VARIABLES

Drug absorption rates may vary widely between individuals and in the same individual at different times and in different physiological states. Drugs taken after a meal are delivered to the small intestine much more slowly than in the fasting state, leading to much lower drug concentrations. In pregnancy, gastric emptying is also delayed, while some drugs may increase or decrease gastric emptying and affect absorption of other drugs.

Drug distribution

Drug distribution varies widely: fat-soluble drugs are stored in adipose tissue, water-soluble drugs are distributed chiefly in the extracellular space, acidic drugs bind strongly to plasma albumin, and basic drugs bind to muscle cells. Hence, variation in plasma albumin concentration, fat content, or muscle mass may all contribute to dose variation. With very highly albumin-bound drugs like warfarin, a small change of albumin concentration can produce a big change in free drug and a dramatic change in drug effect.

Drug metabolism and excretion

Drug metabolism is affected by genetic, environmental, and disease-state factors. Drug acetylation shows genetic polymorphism, whereby individuals fall clearly into either fast or slow acetylator types. Drug oxidation, however, is polygenic, and although a small proportion

of the population can be classified as very slow oxidizers of some drugs, for most drugs and most subjects there is a normal distribution of drug metabolizing capacity.

Many drugs are eliminated by the kidneys without being metabolized. Renal disease or toxicity of other drugs on the kidney can therefore slow excretion of some drugs.

Pharmacodynamics variables

There is significant variation in receptor response to some drugs, especially central nervous system responses—for example, pain and sedation. This can be caused by genetic factors, tolerance, drug interactions, and/or drug dependence.

Disease variables

Both liver disease and kidney disease can have major effects on drug response, chiefly through their effect on metabolism and elimination, respectively (increasing toxicity), but also through their effect on plasma albumin (increasing free drug and thus toxicity). Heart failure can also affect metabolism of drugs with rapid hepatic clearance (for example, lidocaine, propranolol). Respiratory disease and hypothyroidism can impair drug oxidation.

Environmental variables

Many drugs and environmental toxins can induce the hepatic microsomal enzyme—oxidizing system or cytochrome P450 oxygenases, leading to more rapid metabolism and elimination and thus less effective treatment. Environmental pollutants, anesthetic drugs, and other compounds, such as pesticides, can also induce metabolism. Diet and nutritional status also affect pharmacokinetics. For example, in infantile malnutrition and in malnourished elderly populations, drug oxidation rates are decreased, while high-protein diets, charcoal-cooked foods, and certain other foods act as metabolizing-enzyme inducers. Chronic alcohol use induces oxidation of other drugs, but in the presence of high circulating alcohol concentrations, drug metabolism may be inhibited.

ADHERENCE (COMPLIANCE) WITH DRUG TREATMENT

It is often assumed that once the appropriate drug is chosen, the prescription correctly written, and the medication correctly dispensed, that it will be taken correctly and treatment will be successful. Unfortunately, this is very often not the case, and physicians overlook one of the

most important reasons for treatment failure—poor adherence (compliance) with the treatment plan.

There are sometimes valid reasons for poor adherence—the drug may be poorly tolerated, may cause obvious adverse effects, or may be prescribed in a toxic dose. Failure to adhere with such a prescription has been described as “intelligent non-compliance.” Bad prescribing or a dispensing error may also create a problem, which patients may have neither the insight nor the courage to question. Even with good prescribing, failure to adhere to treatment is common. Reasons for non-compliance may be related to the patient, the disease, the doctor, the prescription, the pharmacist or the health system, and can often be avoided.

Patients’ perceptions of the risk and severity of adverse drug reactions may differ from those of the health-care provider and may affect adherence. Low-cost strategies for improving adherence increase effectiveness of health interventions and reduce costs. Such strategies must be tailored to the individual patient. Health-care providers should be familiar with techniques for improving adherence and they should employ systems to assess adherence and to determine what influences it.

Patient reasons

In general, women tend to be more adherent than men, younger patients and the very elderly are less adherent, and people living alone are less adherent than those with partners or spouses. Specific education interventions have been shown to improve adherence. Patient disadvantages such as illiteracy, poor eyesight, or cultural attitudes (for example, preference for traditional or alternative medicines and suspicion of modern medicine) may be very important for some individuals or societies, as may economic factors. Such limitations or attitudes need to be discussed and taken account of.

Disease reasons

Conditions with a known worse prognosis (for example, cancer) or painful conditions (for example, rheumatoid arthritis) elicit better adherence than asymptomatic “perceived as benign” conditions, such as hypertension.

Doctor reasons

Doctors may cause poor adherence in many ways—by failing to inspire confidence in the treatment offered, by giving too little or no explanation, by thoughtlessly prescribing too many medicines, by making errors in prescribing, or by their overall attitude toward the patient.

The doctor–patient interaction

There is considerable evidence that the quality of the doctor–patient interaction is crucial to concordance. “Satisfaction with the interview” is one of the best predictors of good adherence. Patients are often well informed and expect a greater say in their health care. If they are in doubt or dissatisfied, they may turn to alternative options, including “complementary medicine.” There is no doubt that the prescribing doctor has a powerful effect on inspiring confidence and perhaps contributing directly to the healing process.

Prescription reasons

Many aspects of the prescription may lead to non-adherence (non-compliance). It may be illegible or inaccurate; it may get lost; it may not be refilled as intended or instructed for a chronic disease. Also, the prescription may be too complex; the greater the number of different medicines, the poorer the adherence. Multiple doses also decrease adherence, especially if more than two doses per day are given. Not surprisingly, adverse effects like drowsiness, impotence, or nausea reduce adherence, and patients may not admit to the problem.

Pharmacist reasons

The pharmacist’s manner and professionalism, like the doctor’s, may have a positive influence on adherence, or a negative one, raising suspicions or concerns. This has been reported in relation to generic drugs when they are substituted for brand-name drugs. Pharmacist information and advice can be a valuable reinforcement, as long as it agrees with the doctor’s advice.

The health-care system

The health-care system may be the biggest hindrance to adherence. Long waiting times, uncaring staff, an uncomfortable environment, and unreliable drug supplies are all common problems in many settings, and have a major impact on adherence. An important problem is the distance from and the accessibility to the clinic. Some studies have confirmed the obvious, that patients furthest from the clinic are least likely to adhere to treatment in the long term.

Recommendations

- Review the prescription to make sure it is correct.
- Spend time explaining the health problem and the reason for the drug.
- Establish good rapport with the patient.
- Explore problems; for example, difficulty with reading the label or getting the prescription filled.
- Encourage patients to bring their medication to the clinic, so that tablet counts can be done to monitor compliance.
- Encourage patients to learn the names of their medicines, and review their regimen with them. Write notes for them.
- Keep treatment regimens simple.
- Communicate with other health-care professionals to develop a team approach and collaborate on helping and advising the patient.
- Involve the partner or another family member.
- Listen to the patient.

ADVERSE EFFECTS AND INTERACTIONS

Adverse drug reactions

An adverse drug reaction (ADR) may be defined as “any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy...” ADRs are therefore unwanted or unintended effects of a medicine, including idiosyncratic effects,

which occur during its proper use. They differ from accidental or deliberate excessive dosage or drug maladministration (*see* Section 4 for the treatment of poisoning).

ADRs may be directly linked to the properties of the drug in use, the so-called “A” type reactions. An example is hypoglycemia induced by an antidiabetic drug. ADRs may also be unrelated to the known pharmacology of the drug, the “B” type reactions, which include allergic effects—for example, anaphylaxis with penicillins.

Thalidomide marked the first recognized public health disaster related to the introduction of a new drug. It is now recognized that clinical trials, however thorough, cannot be guaranteed to detect all adverse effects likely to be caused by a drug. Health workers are therefore encouraged to record and report to their national pharmacovigilance center any unexpected adverse effects with any drug to help achieve faster recognition of serious related problems.

Major factors predisposing to adverse effects

It is well known that different patients often respond differently to a given treatment regimen. For example, in patients taking combinations of drugs known to interact, only a small number show any clinical evidence of interactions. In addition to the pharmaceutical properties of the drug, therefore, there are characteristics of the patient that predispose to ADRs.

Extremes of age

The very old and the very young are more susceptible to ADRs. Drugs that commonly cause problems in the elderly include hypnotics, diuretics, non-steroidal anti-inflammatory drugs, antihypertensives, psychotropics, and digoxin. All children, particularly neonates, differ from adults in their response to drugs. Some drugs are likely to cause problems in neonates (for example, morphine), but are generally tolerated in children. Other drugs (for example, valproic acid) are associated with increased risk of ADRs in children of all ages. Other drugs associated with problems in children include chloramphenicol (gray baby syndrome), anti-arrhythmics (worsening of arrhythmias), and acetylsalicylic acid (Reye syndrome).

Intercurrent illness

If besides the condition being treated, the patient suffers from another disease, such as kidney, liver, or heart disease, special precautions may be necessary to prevent ADRs. The genetic make-up of the individual patient may also affect predisposition to ADRs.

Drug interactions

Interactions (*see also* Appendix A) may occur between drugs that compete for the same receptor or act on the same physiological system. They may also occur indirectly when a drug-induced disease or a change in fluid or electrolyte balance alters the response to another drug. In addition, interactions may occur when one drug alters the absorption, distribution, or elimination of another drug, such that the amount that reaches the site of action is increased or decreased.

Drug–drug interactions are some of the commonest causes of adverse effects. When two drugs are administered to a patient, they may either act independently of each other, or interact with each other. Interaction may increase or decrease the effects of the drugs concerned and may cause unexpected toxicity. As newer and more potent drugs become available, the number of serious drug interactions is likely to increase. Remember that interactions that modify the effects of a drug may involve non-prescription drugs, non-medicinal chemical agents; social drugs such as alcohol, marijuana, tobacco, and traditional remedies; and certain types of food (for example, grapefruit juice). The physiological changes in individual patients, caused by such factors as age and gender, also influence the predisposition to ADRs resulting from drug interactions.

The following table lists drugs under the designation of specific cytochrome P450 isoforms. A drug appears in a given column if there is published evidence that it is metabolized, at least in part, via the specified isoform. Alterations in the rate of the metabolic reaction catalyzed by that isoform are likely to have effects on the pharmacokinetics of the drug.

Table 1. Pharmaceuticals, as metabolized by isoform

SUBSTRATES						
CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP2D6	CYP2E1	CYP3A4, 5, 7
	Cyclophosphamide Efavirenz Methadone	Amitriptyline Clomipramine Cyclophosphamide Diazepam Phenobarbital Phenytoin	Ibuprofen Phenytoin Sulfamethoxazole Tamoxifen Warfarin	Amitriptyline Clomipramine Codeine Haloperidol Tamoxifen Timolol	Alcohol Paracetamol	Amlodipine Chlorphenamine Cyclosporin Diazepam Erythromycin Haloperidol Indinavir Methadone Nifedipine Quinidine Quinine Ritonavir Saquinavir Tamoxifen Verapamil Vincristine
INHIBITORS						
1A2	2B6	2C19	2C9	2D6	2E1	3A4
Ciprofloxacin			Isoniazid	Chlorphenamine Clomipramine Haloperidol Methadone Quinidine Ritonavir		Erythromycin Grapefruit juice Indinavir Nelfinavir Ritonavir Verapamil
INDUCERS						
1A2	2B6	2C19	2C9	2D6	2E1	3A4
Tobacco	Phenobarbital Rifampicin		Rifampicin		Alcohol Isoniazid	Carbamazepine Phenobarbital Phenytoin Rifampicin

Incompatibilities between drugs and intravenous fluids

Drugs should not be added to blood, amino acid solutions, or fat emulsions. Certain drugs, when added to intravenous fluids, may be inactivated by pH changes, by precipitation, or by chemical reaction. Benzylpenicillin and ampicillin lose potency after 6–8 hours if added to dextrose solutions due to the acidity of these solutions. Some drugs bind to plastic containers and tubing; for example, diazepam and insulin. Aminoglycosides are incompatible with penicillins and heparin. Hydrocortisone is incompatible with heparin, tetracycline, and chloramphenicol.

Adverse effects caused by traditional medicines

Patients who have been, or are taking, traditional herbal remedies may develop ADRs. In these types of preparations, it is not always easy to identify the responsible plant or plant constituent. Refer to the drug and toxicology information service if available or to suitable literature.

The effect of food on drug absorption

Food delays gastric emptying and reduces the rate of absorption of many drugs; the total amount of drug absorbed may or may not be reduced. However, some drugs are taken with food, either to increase absorption or to decrease the irritant effect on the stomach.

PRESCRIPTION WRITING

A prescription is an instruction from a prescriber to a dispenser. The prescriber is not always a doctor but can be a paramedical worker, such as a medical assistant, a midwife, or a nurse. The dispenser is not always a pharmacist, but can be a pharmacy technician, an assistant, or a nurse. Every country has its own standards for the minimum information required for a prescription, and its own laws and regulations to define which drugs require a prescription and who is entitled to write one. Many countries have separate regulations for prescriptions for controlled drugs such as opioid analgesics.

The following guidelines will help ensure that prescriptions are correctly interpreted and leave no doubt about the intention of the prescriber. The guidelines are relevant for primary care prescribing; they may, however, be adapted for use in hospitals or other specialist units.

Prescription form

The most important requirement is that the prescription be clear. It should be legible and indicate precisely what should be given. The local language is preferred.

The following details should be shown on the form:

- The prescriber's name, address, and telephone number. This will allow either the patient or the dispenser to contact the prescriber for any clarification or potential problem with the prescription.
- Date of the prescription. In many countries, the validity of a prescription has no time limit, but in some countries pharmacists do not dispense drugs on prescriptions older than 3–6 months.
- Name, form, and strength of the drug. The International Nonproprietary Name of the drug should always be used. If there is a specific reason to prescribe a special brand, the trade name can be added. The pharmaceutical form (for example, “tablet,” “oral solution,” “eye ointment”) should also be stated.
- The strength of the drug should be stated in standard units using abbreviations that are consistent with the *Système International* (SI).
- “Microgram” and “nanogram” should not, however, be abbreviated. Also, “units” should not be abbreviated. Avoid decimals whenever possible. If this is unavoidable, a zero should be written in front of the decimal point.
- Specific areas for filling in details about the patient, including name, address, and age.

Directions

Directions specifying the route, dose, and frequency should be clear and explicit; use of phrases such as “take as directed” or “take as before” should be avoided.

For preparations that are to be taken on an “as required” basis, the minimum dose interval should be stated together with, where relevant, the maximum daily dose. It is good practice to

qualify such prescriptions with the purpose of the medication (for example, “every 6 hours as required for pain,” “at night as required to sleep”).

It is good practice to explain the directions to the patient; these directions will then be reinforced by the label on the medicinal product and possibly by appropriate counseling by the dispenser. It may be worthwhile giving a written note for complicated regimens, although it must be borne in mind that the patient may lose the separate note.

Quantity to be dispensed

The quantity of the medicinal product to be supplied should be stated such that it is not confused with either the strength of the product or the dosage directions. Alternatively, the length of the treatment course may be stated (for example, “for 5 days”).

Wherever possible, the quantity should be adjusted to match the pack sizes available.

For liquid preparations, the quantity should be stated in milliliters (abbreviated as “mL”) or liters (abbreviated as “L”; the lowercase letter “l” should not be used, to avoid confusion with the numeral “1”).

Narcotics and controlled substances

The prescribing of a medicinal product that may be abused requires special attention and may be subject to specific statutory requirements. Practitioners may need to be authorized to prescribe controlled substances; in such cases it might be necessary to indicate details of the authority on the prescription. In particular, the strength, directions, and the quantity of the controlled substance to be dispensed should be stated clearly, with all quantities written in words as well as in figures to prevent alteration. Other details such as patient particulars and date should also be filled in carefully to avoid alteration.

Sample prescription



Ministry of public health
General curative directorate
Hospital.....

Name of patient:		Age:	Gender:	Weight:
Register No:		Ward:	Date:	
Clinical Records				
	Name of Doctor: Signature:			

SECTION 1: Anesthetics

To produce a state of prolonged full surgical anesthesia reliably and safely, a variety of drugs is needed. Special precautions and close monitoring of the patient are also required.

Anesthetic drugs may be fatal if used inappropriately and should be used by non-specialized personnel only as a last resort. Irrespective of whether a general or conduction (regional or local) anesthetic technique is used, it is essential that equipment for intubation and mechanically assisted ventilation are available. A full preoperative assessment is required, including, if necessary, appropriate fluid replacement.

Anesthesia may be induced with an intravenous barbiturate, parenteral ketamine, or a volatile agent. Maintenance is with inhalational agents often supplemented by other drugs given intravenously. Specific drugs may be used to produce muscle relaxation. Various drugs may be needed to modify normal physiological functions or otherwise maintain the patient in a satisfactory condition during surgery.

Long-term medication

The risk of stopping long-term medication before surgery may be greater than the risk of continuing it. It is essential that the anesthetist be told of all drugs that the patient is (or has been) taking; for further advice, *see* Section 10.2 (Oral anticoagulants), Section 18.1 (Corticosteroids), Section 18.3.1 (Hormonal contraceptives), and Section 18.5 (Diabetic patients).

LML strengths and dosage forms are marked in *italic* and with an asterisk.

1.1 GENERAL ANESTHETICS AND OXYGEN

Intravenous agents

Intravenous anesthetics may be used alone to produce anesthesia for short surgical procedures but are more commonly used for induction only. They can produce apnea and hypotension, and thus facilities for adequate resuscitation must be available. They are contraindicated if the anesthetist is not confident of being able to maintain an airway. Before intubation is attempted, a muscle relaxant must be given. Individual requirements vary considerably; lesser dosage is indicated in the elderly, debilitated, or hypovolemic patients.

Intravenous induction using **thiopental** is rapid and excitement does not usually occur. Anesthesia persists for about 4–7 minutes; large or repeated doses severely depress respiration and delay recovery.

Anesthesia with **ketamine** persists for up to 15 minutes after a single intravenous injection and is characterized by profound analgesia. It may be used as the sole agent for diagnostic and minor surgical interventions. Sub-anesthetic concentrations of ketamine may be used to provide analgesia for painful procedures of short duration such as the dressing of burns, radiotherapeutic procedures, marrow sampling, and minor orthopedic procedures. Recovery from ketamine anesthesia is associated with a high incidence of hallucinations and other emergence reactions, such as delirium. Ketamine is of particular value in children, in whom hallucinations are believed to be less significant.

Volatile inhalational agents

One of the volatile anesthetics, ether or halothane (with or without nitrous oxide), must be used for induction when intravenous agents are contraindicated and particularly when intubation is likely to be difficult. Full muscle relaxation is achieved in deep anesthesia with ether. Excess bronchial and salivary secretion can be avoided by premedication with atropine. Laryngeal spasm may occur during induction and intubation. Localized capillary bleeding can be troublesome, and postoperative nausea and vomiting is frequent; recovery time is slow, particularly after prolonged administration.

If intubation is likely to be difficult, **halothane** is preferred. It does not augment salivary or bronchial secretions, and the incidence of postoperative nausea and vomiting is low. Severe hepatitis, which may be fatal, sometimes occurs; it is more likely in patients who are repeatedly anesthetized with halothane within a short period of time.

Inhalational gases

Nitrous oxide is used for the maintenance of anesthesia. It is too weak to be used alone, but it allows the dosage of other anesthetic agents to be reduced. It has a strong analgesic action.

Oxygen should be added routinely during anesthesia with inhalational agents, even when air is used as the carrier gas, to protect against hypoxia.

Oxygen is also used in the management of anaphylaxis (Section 3), myocardial infarction (Section 12.5), and severe acute asthma (Section 25.1).

Identification of cylinders for inhalation gases

An ISO standard (International Standard 32, Gas Cylinders for Medical Use, 1977) requires that cylinders containing nitrous oxide should bear the name of the contents in legible and permanent characters, and preferably also the chemical symbol, N_2O . The neck, from the valve to the shoulder, should be colored blue. Cylinders containing oxygen intended for medical use should bear the name of the contents in legible and permanent characters, and preferably also the chemical symbol, O_2 . The neck, from the valve to the shoulder, should be colored white. Cylinders containing nitrous oxide and oxygen mixtures should be similarly labeled, and the neck colored white and blue.

- **Halothane**

Halothane is a representative volatile anesthetic. Various drugs can serve as alternatives.

- **Dosage form**

- Inhalation gas in 250 ml bottle
- **Uses**
 - Induction and maintenance of anesthesia
- **Contraindications**
 - History of unexplained jaundice or pyrexia following previous exposure to halothane
 - Family history of malignant hyperthermia
 - Raised cerebrospinal fluid pressure
 - Porphyria
- **Precautions**
 - Anesthetic history should be carefully taken to determine previous exposure and previous reactions to halothane (at least 3 months should be allowed to elapse between each re-exposure)
 - Avoid for dental procedures in patients under 18 years unless treated in hospital (high risk of arrhythmias)
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A
- **Dose**
 - Induction: Using a specifically calibrated vaporizer, gradually increase inspired gas concentration to 2–4% (**ADULT**) or 1.5–2% (**CHILD**), in oxygen or nitrous oxide–oxygen.
 - Maintenance: **ADULT** and **CHILD**, 0.5–2%
- **Adverse effects**
 - Arrhythmias
 - Bradycardia
 - Respiratory depression
 - Hepatic damage

- **Isoflurane**

- **Dosage form**

- Inhalation gas in 250 ml bottle

- **Uses**

- Induction and maintenance of anesthesia, and following induction with an intravenous anesthetic

- **Contraindications**

- Patient susceptible to malignant hyperthermia

- **Precautions**

- Raised intracranial pressure
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A (Anesthetics, general)

- **Dose**

- Induction of anesthesia: Using specifically calibrated vaporizer, in oxygen or nitrous oxide–oxygen, increased gradually from 0.5% to 3%
 - Maintenance of anesthesia: Using specifically calibrated vaporizer, 1–2.5% in nitrous oxide–oxygen; an additional 0.5–1% may be required when given with oxygen alone
 - Cesarean section: 0.5–0.75% in nitrous oxide–oxygen

- **Adverse effects**

- Malignant hyperthermia
 - Hepatotoxicity in those sensitized to halogenated anesthetics
 - In children with neuromuscular disease, inhalation anesthetics are very rarely associated with hyperkalemia, resulting in cardiac arrhythmias and death.
 - Cardiorespiratory depression, hypotension, and arrhythmias
 - Mood changes that can last for several days

- Cough, breath holding, and laryngospasm
- Heart arrhythmia, particularly in young patients
- Systemic arterial pressure and cardiac output can fall, owing to a decrease in systemic vascular resistance

- **Ketamine**

- **Dosage form**

- Injection: 50 mg (as hydrochloride)/ml in 10 ml vial

- **Uses**

- Induction and maintenance of anesthesia
- Analgesia for painful procedures of short duration

- **Contraindications**

- Thyrotoxicosis
- Hypertension (including pre-eclampsia)
- History of cerebrovascular accident, cerebral trauma, intracerebral mass or hemorrhage, or other cause of raised intracranial pressure
- Eye injury and increased intraocular pressure
- Psychiatric disorders, particularly hallucinations
- Porphyria

- **Precautions**

- Supplementary analgesia is often required in surgical procedures involving visceral pain pathways (morphine may be used but addition of nitrous oxide will often suffice).
- Administer an anti-sialogogue to prevent excessive salivation leading to respiratory difficulties; during recovery, patient must remain undisturbed but under observation.
- Pregnancy: Appendix B.
- **Interactions:** Appendix A.
- **Skilled tasks:** Warn patient not to perform skilled tasks (such as operating machinery or driving) for 24 hours, and to avoid alcohol for 24 hours.

- **Dose**

- Anesthesia, by intramuscular injection*

- **ADULT and CHILD:** Induction, 6.5–13 mg/kg (10 mg/kg usually produces 12–25 minutes of anesthesia)
 - Maintenance: 50–100% of induction dose as required

- Anesthesia, by intravenous injection*

- **ADULT and CHILD:** Induction, over at least 1 minute, 1–4.5 mg/kg (2 mg/kg usually produces 5–10 minutes of anesthesia)
 - Maintenance: 50–100% of induction dose as required

- Anesthesia, by intravenous infusion*

- **ADULT and CHILD:** Induction, of a solution containing 1 mg/ml, total induction dose 0.5–2 mg/kg
 - Maintenance (using micro-drip infusion): 10–45 micrograms/kg/min., rate adjusted according to response

- Analgesia, by intramuscular injection*

- **ADULT and CHILD:** Initially 4 mg/kg

Note: For diagnostic procedures and other procedures not involving intense pain.

Dilution and administration: According to manufacturer's directions.

- **Adverse effects**

- Hallucinations and other emergence reactions during recovery may occur, possibly accompanied by irrational behavior (effects rarely persist for more than a few hours but can recur at any time within 24 hours).
 - Transient elevation of pulse rate and blood pressure common.
 - Arrhythmias have occurred.
 - Hypotension and bradycardia occasionally reported.

- **Oxygen**

- **Dosage form**

- Inhalation (medicinal gas)

- **Uses**

- To maintain an adequate oxygen tension in inhalational anesthesia

- **Precautions**

- **Interactions:** Appendix A

- **Dose**

- Concentration of oxygen in inspired anesthetic gases should never be less than 21%

- **Adverse effects**

- Concentrations greater than 80% have a toxic effect on the lungs, leading to pulmonary congestion, exudation, and atelectasis.

Caution: FIRE HAZARD. Avoid use of cautery when oxygen is used with ether; reducing valves on oxygen cylinders must not be greased (risk of explosion).

- **Propofol**

- **Dosage form**

- Injection 10 mg/ml, in 20 ml, and 100 ml ampoules

- **Uses**

- Induction of anesthesia, maintenance of anesthesia, sedation of ventilated patients
 - Induction of sedation for surgical and diagnostic procedures

- **Contraindications**

- If the anesthetist is not confident of being able to maintain the airway (for example, in the presence of a tumor in the pharynx or larynx).

- Extreme care is required in surgery of the mouth, pharynx, or larynx and in patients with acute circulatory failure (shock) or fixed cardiac output.
 - Children under 16 years receiving intensive care because of the risk of propofol infusion syndrome (potentially fatal effects, including metabolic acidosis, cardiac failure, rhabdomyolysis, hyperlipidemia, and hepatomegaly).
- **Precautions**
- Cardiac impairment
 - Respiratory impairment
 - Elderly
 - Hypovolemia
 - Epilepsy
 - Hypotension
 - Raised intracranial pressure
 - Monitor blood-lipid concentration if risk of fat overload or if sedation longer than 3 days
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Breast-feeding: Appendix C
 - Pregnancy: Appendix B
 - **Interactions:** Appendix A (Anesthetics, general)
- **Dose**
- Anesthesia, by slow intravenous injection or intravenous infusion*
- **ADULT** under 55 years: Induction using 0.5% or 1% injection, 1.5–2.5 mg/kg at a rate of 20–40 mg every 10 seconds until response
 - **ADULT** over 55 years or **DEBILITATED:** Induction using 0.5% or 1% injection, 1–1.5 mg/kg at a rate of 20 mg every 10 seconds until response
 - **CHILD** 1 month–18 years: Adjust dose according to age, weight, and response. Induction using 0.5% or 1% injection, usual dose in **CHILD** 1 month–17 years: 2.5–4 mg/kg. Usual dose in **CHILD** 17–18 years: 1.5–2.5 mg/kg at a rate of 20–40 mg every 10 seconds until response.

Maintenance of anesthesia using 1% injection by intravenous infusion

- **ADULT:** 4–12 mg/kg/hour (3–6 mg/kg/hour in **ELDERLY** or **DEBILITATED**) or *by slow intravenous injection*, 25–50 mg repeated according to response

Maintenance of anesthesia using 1% injection by continuous intravenous infusion

- **CHILD** 1 month–18 years: Adjust dose according to age, body weight, and response
- Usual dose in **CHILD** 1 month–17 years: 9–15 mg/kg/hour
- Usual dose in **CHILD** 17–18 years: 1.5–2.5 mg/kg/hour, adjusted according to response

Sedation of ventilated patients in intensive care using 1% injection, by intravenous infusion

- **ADULT** and **CHILD** over 16 years: 0.3–4 mg/kg/hour

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

- **ADULT:** Initially by *slow intravenous injection* over 1–5 minutes, 0.5–1 mg/kg, dose and rate of administration adjusted according to desired level of sedation and response
- **CHILD** 1 month–18 years: *By slow intravenous injection*, dose and rate of administration adjusted according to desired level of sedation and response. Usual dose in **CHILD** 1 month–17 years: 1–2 mg/kg over 1–5 minutes

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

- **ADULT:** 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response (additionally, if rapid increase in sedation required, *by slow intravenous injection*, 10–20 mg). Patients over 55 years or **DEBILITATED** may require lower dose and rate of administration.
- **CHILD** 17–18 years: Dose and rate of administration adjusted according to desired level of sedation response; usual dose 1.5–4.5 mg/kg/hour

(additionally, if rapid increase in sedation required, by *slow intravenous injection* 10–20 mg)

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

- **ADULT:** 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response (additionally, if rapid increase in sedation required, by *slow intravenous injection*, 10–20 mg). Patients over 55 years or **DEBILITATED** may require lower dose and rate of administration.
- **CHILD** 1 month–18 years: Dose and rate of administration adjusted according to desired level of sedation and response. Usual dose in **CHILD** 1 month–17 years: 1.5–9 mg/kg/hour (additionally, if rapid increase in sedation required, by *slow intravenous injection*, max. 1 mg/kg). Usual dose in **CHILD** 17–18 years: 1.5–4.5 mg/kg/hour (additionally, if rapid increase in sedation required, by *slow intravenous injection*, 10–20 mg/kg).

○ **Adverse effects**

- Rarely, convulsions, anaphylaxis, and delayed recovery from anesthesia can occur after propofol administration; the onset of convulsions can be delayed.
- Hypotension, tachycardia, flushing
- Transient apnea, hyperventilation, coughing, and hiccup during induction
- Headache
- Less commonly thrombosis, phlebitis
- Rarely arrhythmia, headache, vertigo, shivering, euphoria
- Very rarely pancreatitis, pulmonary edema, sexual disinhibition, and discoloration of urine
- Serious and sometimes fatal side effects reported with prolonged infusion of doses exceeding 5 mg/kg/hour, including metabolic acidosis, rhabdomyolysis, hyperkalemia, and cardiac failure. Dystonia and dyskinesia have also been reported.

- **Thiopental**

Thiopental is a representative intravenous anesthetic. Various drugs can serve as alternatives.

- **Dosage form**

- Injection ampoules containing 500 mg and 1 g thiopental sodium

- **Uses**

- Induction of anesthesia prior to administration of inhalational anesthetic
- Anesthesia of short duration

- **Contraindications**

- Inability to maintain airway
- Hypersensitivity to barbiturates
- Cardiovascular disease
- Dyspnea or obstructive respiratory disease
- Myotonic dystrophy
- Porphyria

- **Precautions**

- Reconstituted solution is highly alkaline (extravasation can result in extensive tissue necrosis and sloughing).
- Cardiovascular disease
- Intra-arterial injection causes intense pain and may result in arteriospasm.
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A
- **Skilled tasks:** Warn patient not to perform skilled tasks (such as operating machinery or driving) for 24 hours, and to avoid alcohol for 24 hours.

- **Dose**

Induction, by intravenous injection, usually as a 2.5% (25 mg/ml) solution over 10–15 seconds

- **ADULT:** 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 (max. 500 mg)
- **CHILD:** 2–7 mg/kg, repeated if necessary according to response after 60 seconds

Reconstitution

- Solutions containing 25 mg/ml should be freshly prepared by mixing 20 ml of water for injections with the contents of the 0.5 g ampoule or 40 ml of water for injections with that of the 1 g ampoule. Any solution made up over 24 hours previously or in which cloudiness, precipitation, or crystallization is evident should be discarded.

○ **Adverse effects**

- Rapid injection may result in severe hypotension and hiccup.
- Arrhythmias and myocardial depression
- Cough, laryngeal spasm, and sneezing
- Allergic reactions including rash, injection-site reactions

1.2 Local anesthetics

Drugs used for conduction anesthesia (also termed local or regional anesthesia) act by causing a reversible block to conduction along nerve fibers. Local anesthetics are used very widely in dental practice, for brief and superficial interventions, for obstetric procedures, and for specialized techniques of regional anesthesia calling for highly developed skills. Where patient cooperation is required, the patient must be psychologically prepared to accept the proposed procedure.

Facilities and equipment for resuscitation should be readily available at all times. Local anesthetic injections should be given slowly in order to detect inadvertent intravascular injection.

Local infiltration

Many simple surgical procedures that neither involve the body cavities nor require muscle relaxation can be performed under local infiltration anesthesia. Lower-segment cesarean section can also be performed under local infiltration anesthesia. The local anesthetic drug of choice is **lidocaine** 0.5% with or without epinephrine. No more than 4 mg/kg of plain lidocaine or 7 mg/kg of lidocaine with epinephrine should be administered on any one occasion. The addition of **epinephrine** (adrenaline) diminishes local blood flow, slows the rate of absorption of the local anesthetic, and prolongs its effect. Care is necessary when using epinephrine for this purpose since, in excess, it may produce ischemic necrosis. **It should NOT be added to injections used in digits or appendages.**

Surface anesthesia

Topical preparations of **lidocaine** are available and topical eyedrop solutions of **tetracaine** are used for local anesthesia of the cornea and conjunctiva.

Regional block

A regional nerve block can provide safe and effective anesthesia but its execution requires considerable training and practice. Nevertheless, where the necessary specialist skills are available, techniques such as axillary or ankle blocks can be invaluable. Either **lidocaine** 1% or **bupivacaine** 0.5% is suitable. Bupivacaine has the advantage of a longer duration of action.

Spinal anesthesia

This is one of the most useful of all anesthetic techniques and can be used widely for surgery of the abdomen and the lower limbs. It is a major procedure requiring considerable training and practice. Either **lidocaine** 5% in glucose or **bupivacaine** 0.5% in glucose can be used but the latter is often chosen because of its longer duration of action.

- **Bupivacaine**

Bupivacaine is a representative local anesthetic. Various drugs can serve as alternatives.

- **Dosage form**

- Injection: 0.25%; 0.5% (hydrochloride) in 10 ml ampoules

- **Uses**

- Infiltration anesthesia
- Peripheral and sympathetic nerve block
- Caudal and epidural anesthesia
- Postoperative pain relief

- **Contraindications**

- Adjacent skin infection or inflamed skin
- Concomitant anticoagulant therapy
- Severe anemia or heart disease
- Epidural anesthesia in dehydrated or hypovolemic patients

- **Precautions**

- Respiratory impairment
- Epilepsy
- Porphyria
- Myasthenia gravis
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B
- **Interactions:** Appendix A

- **Dose**

- Local infiltration, using 0.25% solution: **ADULT**, up to 150 mg (up to 60 ml)
- Peripheral nerve block, using 0.25% solution: **ADULT**, up to 150 mg (up to 60 ml)
- Peripheral nerve block, using 0.5% solution: **ADULT**, up to 150 mg (up to 30 ml)

- Lumbar epidural block in surgery, using 0.5% solution: **ADULT**, 50–100 mg (10–20 ml)
- Lumbar epidural block in labor, using 0.25–0.5% solution: **ADULT** (female), up to 60 mg (up to 12 ml)
- Caudal block in surgery, using 0.25–0.5% solution: **ADULT**, up to 150 mg (up to 30 ml)
- Caudal block in labor, using 0.25–0.5% solution: **ADULT** (female), up to 100 mg (max. 20 ml)

Note: Use lower doses for debilitated or elderly patients or in epilepsy or acute illness. **Do not use solutions containing preservatives for spinal, epidural, caudal, or intravenous regional anesthesia.**

○ **Adverse effects**

- With excessive dosage or following intravascular injection: light-headedness, dizziness, blurred vision, restlessness, tremors, and, occasionally, convulsions rapidly followed by drowsiness, unconsciousness, and respiratory failure
- Cardiovascular toxicity includes hypotension, heart block, and cardiac arrest; hypersensitivity and allergic reactions also occur.
- Epidural anesthesia occasionally complicated by urinary retention, fecal incontinence, headache, backache, or loss of perineal sensation
- Very rarely transient paresthesia and paraplegia

● **Lidocaine**

Lidocaine is a representative local anesthetic. Various drugs can serve as alternatives.

○ **Dosage form**

- Injection: 1%; 2% (hydrochloride) in 2 ml ampoule and 20 mg/ml in 5 ml vial
- Injection for spinal anesthesia: 5% (hydrochloride) in 2 ml ampoule to be mixed with 7.5% glucose solution
- *Oral topical spray: 10% in 100 ml bottle**
- *Oral topical cream: 2% in 25 g tube**
- Topical gel: 2% and 4% topical gels (hydrochloride)

- **Uses**
 - Surface anesthesia of mucous membranes
 - Infiltration anesthesia
 - Peripheral and sympathetic nerve block
 - Dental anesthesia
 - Spinal anesthesia
 - Intravenous regional anesthesia
 - Arrhythmias: Section 12.2
- **Contraindications**
 - Adjacent skin infection, inflamed skin
 - Concomitant anticoagulant therapy
 - Severe anemia or heart disease
 - Spinal or epidural anesthesia in dehydrated or hypovolemic patients
- **Precautions**
 - Bradycardia, impaired cardiac conduction
 - Severe shock
 - Respiratory impairment
 - Epilepsy
 - Porphyria
 - Myasthenia gravis
 - Avoid (or use with great care) solutions containing epinephrine (adrenaline) for ring block of digits or appendages (risk of ischemic necrosis)
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Breast-feeding: Appendix C
 - Pregnancy: Appendix B
 - **Interactions:** Appendix A
- **Dose**

Plain solutions

- Local infiltration and peripheral nerve block, using 0.5% solution, **ADULT:** Up to 250 mg (up to 50 ml)
- Local infiltration and peripheral nerve block, using 1% solution, **ADULT:** Up to 250 mg (up to 25 ml)
- Surface anesthesia of pharynx, larynx, trachea, using 4% solution, **ADULT:** 40–200 mg (1–5 ml)
- Surface anesthesia of urethra, using 4% solution, **ADULT:** 400 mg (10 ml)
- Spinal anesthesia, using 5% solution (with glucose 7.5%), **ADULT:** 50–75 mg (1–1.5 ml)

Solutions containing epinephrine

- Local infiltration and peripheral nerve block, using 0.5% solution with epinephrine, **ADULT:** Up to 400 mg (up to 80 ml)
- Local infiltration and peripheral nerve block, using 1% solution with epinephrine, **ADULT:** Up to 400 mg (up to 40 ml)
- Dental anesthesia, using 2% solution with epinephrine, **ADULT:** 20–100 mg (1–5 ml)

Notes: Maximum safe doses of lidocaine for **ADULT** and **CHILD** are 0.5% or 1% lidocaine, 4 mg/kg; 0.5% or 1% lidocaine + epinephrine 5 micrograms/ml (1 in 200 000), 7 mg/kg.

Use lower doses for debilitated or elderly patients or in epilepsy or acute illness. Do not use solutions containing preservatives for spinal, epidural, caudal, or intravenous regional anesthesia.

○ **Adverse effects**

- With excessive dosage or following intravascular injection: light-headedness, dizziness, blurred vision, restlessness, tremors and, occasionally, convulsions rapidly followed by drowsiness, unconsciousness, and respiratory failure
- Cardiovascular toxicity includes hypotension, heart block, and cardiac arrest; hypersensitivity and allergic reactions also occur.
- Epidural anesthesia occasionally complicated by urinary retention, fecal incontinence, headache, backache, or loss of perineal sensation
- Very rarely transient paresthesia and paraplegia

- **Lidocaine + epinephrine (adrenaline)**

Lidocaine is a representative local anesthetic. Various medicines can serve as alternatives.

- **Dosage form**

- Dental cartridge: lidocaine 1% and 2% (hydrochloride) + epinephrine 1:80,000
- Injection: 1%; 2% (hydrochloride) + epinephrine 1:200,000 in vial

- **Uses**

- Surface anesthesia of mucous membranes
- Infiltration anesthesia
- Peripheral and sympathetic nerve block
- Dental anesthesia
- Spinal anesthesia
- Intravenous regional anesthesia
- Arrhythmias: Section 12.2.

1.3 Preoperative medication and sedation for short-term procedures

Pre-anesthetic medication is often advisable prior to both conduction and general anesthetic procedures.

Sedatives improve the course of subsequent anesthesia in apprehensive patients. **Diazepam** and **promethazine** are effective. Diazepam can be administered by mouth, by rectum, or by intravenous injection. Promethazine, which has antihistaminic and anti-emetic properties as well as a sedative effect, is of particular value in children.

A potent analgesic such as **morphine** should be administered preoperatively to patients in severe pain or for analgesia during and after surgery.

Anticholinergic (or more correctly, antimuscarinic) drugs such as **atropine** are also used before general anesthesia. They inhibit excessive bronchial and salivary secretions induced,

in particular, by ether and ketamine. Intramuscular administration is most effective, but oral administration is more convenient in children. Lower doses should be used in cardiovascular disease or hyperthyroidism.

- **Atropine**

- **Dosage form**

- Injection: 0.5 mg/ml* and 1 mg/ml in 1 ml ampoule (as sulfate)

- **Uses**

- To inhibit salivary secretions
- To inhibit arrhythmias resulting from excessive vagal stimulation
- To block the parasympathomimetic effects of anticholinesterases such as neostigmine
- Organophosphate poisoning: Section 4.2
- Mydriasis and cycloplegia: Section 21.5

- **Contraindications**

- Angle-closure glaucoma
- Myasthenia gravis
- Paralytic ileus, pyloric stenosis
- Prostatic enlargement

- **Precautions**

- Down syndrome
- Children
- Elderly
- Ulcerative colitis
- Diarrhea
- Hyperthyroidism
- Heart failure or hypertension
- Pyrexia
- Breast-feeding: Appendix C

- Pregnancy: Appendix B
- **Interactions:** Appendix A
- **DURATION OF ACTION:** Since atropine has a shorter duration of action than neostigmine, late unopposed bradycardia may result; close monitoring of the patient is necessary.

○ **Dose**

Premedication, by intravenous injection

- **ADULT:** 300–600 micrograms immediately before induction of anesthesia
- **CHILD:** 20 micrograms/kg (max. 600 micrograms)

Premedication, by subcutaneous or intramuscular injection

- **ADULT:** 300–600 micrograms 30–60 minutes before induction
- **CHILD:** 20 micrograms/kg (max. 600 micrograms)

Intraoperative bradycardia, by intravenous injection

- **ADULT:** 300–600 micrograms (larger doses in emergencies)
- **CHILD** 1–12 years: 10–20 micrograms/kg

Control of muscarinic side effects of neostigmine in reversal of competitive neuromuscular block, by intravenous injection

- **ADULT:** 0.6–1.2 mg
- **CHILD** under 12 years (but rarely used): 20 micrograms/kg (max. 600 micrograms) with neostigmine 50 micrograms/kg

○ **Adverse effects**

- Dry mouth
- Blurred vision, photophobia
- Flushing and dryness of skin, rash
- Difficulty in micturition
- Less commonly arrhythmias, tachycardia, and palpitations
- Confusion (particularly in the elderly)
- Heat prostration and convulsions, especially in febrile children

- **Diazepam**

Diazepam is a representative benzodiazepine. Various drugs can serve as alternatives.

- **Dosage form**

- Injection: 5 mg/ml in 2 ml ampoule
- Tablet: 2 mg, 5 mg, and 10 mg

- **Uses**

- Premedication before major or minor surgery
- Sedation with amnesia for endoscopic procedures and surgery under local anesthesia
- In combination with pethidine when anesthetic not available, for emergency reduction of fractures
- Epilepsy: Section 5
- Anxiety disorders: Section 24.3

- **Contraindications**

- Central nervous system depression or coma
- Shock
- Respiratory depression
- Acute pulmonary insufficiency
- Sleep apnea
- Acute alcohol intoxication
- Severe hepatic impairment
- Marked neuromuscular respiratory weakness including unstable myasthenia gravis

- **Precautions**

- Respiratory disease
- Muscle weakness and myasthenia gravis
- History of alcohol or drug abuse
- Marked personality disorder
- Elderly or debilitated patients (adverse effects more common in these groups)

- Close observation required until full recovery after sedation
 - Porphyria
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Breast-feeding: Appendix C
 - Pregnancy: Appendix B
 - **Interactions:** Appendix A
 - **Skilled tasks:** Warn patient not to perform skilled tasks (for example, operating machinery or driving) for 24 hours.
- **Dose**
- Premedication, *by mouth* 2 hours before surgery, **ADULT** and **CHILD** over 12 years, 5–10 mg
 - Sedation, *by slow intravenous injection* immediately before procedure, **ADULT** and **CHILD** over 12 years: 200 micrograms/kg
 - **Administration:** Absorption following intramuscular injection is slow and erratic; this route should only be used if neither oral nor intravenous administration is possible. Slow intravenous injection into large vein reduces risk of thrombophlebitis. Resuscitation equipment must be available.
- **Adverse effects**
- Central nervous system effects common and include drowsiness, sedation, confusion, amnesia, vertigo, and ataxia
 - Hypotension, bradycardia, or cardiac arrest, particularly in elderly or severely ill patients; also paradoxical reactions, including irritability, excitability, hallucinations, and sleep disturbances
 - Pain and thromboembolism on intravenous injection

- **Midazolam**

- **Dosage form**

- Injection: 1 mg/ml in 1 ml ampoule (as hydrochloride)

- **Uses**

- Conscious sedation for procedures
 - Sedation in intensive care
 - Sedation in anesthesia
 - Premedication
 - Induction of anesthesia
 - Status epilepticus

- **Contraindications**

- Marked neuromuscular respiratory weakness, including unstable myasthenia gravis
 - Severe respiratory depression
 - Acute pulmonary insufficiency
 - Acute pulmonary failure
 - Sleep apnea syndrome

- **Precautions**

- Cardiac disease
 - Respiratory disease
 - Myasthenia gravis
 - Neonates
 - Children (particularly if cardiovascular impairment)
 - Risk of airways obstruction and hypoventilation in children under 6 months (monitor respiratory rate and oxygen saturation)
 - History of drug or alcohol abuse
 - Reduce dose in elderly and debilitated.
 - Risk of severe hypotension in hypovolemia, vasoconstriction, hypothermia
 - Avoid prolonged use (and abrupt withdrawal thereafter)
 - Concentration of midazolam in children under 15 kg not to exceed 1 mg/ml

- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B.
- **Interactions:** Appendix A

○ **Dose**

Conscious sedation for procedures, by slow intravenous injection (approx. 2 mg/min)

- **ADULT:** 5–10 minutes before procedure, initially 2–2.5 mg (**ELDERLY** 0.5–1 mg), increased if necessary in steps of 1 mg (**ELDERLY** 0.5–1 mg); usual total dose 3.5–5 mg (max. 7.5 mg), **ELDERLY** maximum 3.5 mg
- **CHILD** 1 month–18 years: 500 micrograms/kg (max. 20 mg) 30–60 minutes before procedure

Sedative in combined anesthesia

- **ADULT:** By intravenous injection, 30–100 micrograms/kg repeated as required or by continuous intravenous infusion, 30–100 micrograms/kg/hour (**ELDERLY:** lower doses needed).
- **CHILD:** Not recommended

Premedication, by deep intramuscular injection

- **ADULT** over 18 years: 70–100 micrograms/kg (**ELDERLY** or **DEBILITATED:** 25–50 micrograms/kg), 20–60 minutes before induction

Premedication, by intravenous injection

- **ADULT** over 18 years: 1–2 mg, 5–30 minutes before procedure, repeated as required (**ELDERLY** or **DEBILITATED:** 0.5 mg, repeat dose slowly as required)

Premedication, by rectum (by means of a plastic applicator fixed on the end of the syringe)

- **CHILD:** 6 months–12 years 300–500 micrograms/kg, 15–30 minutes before induction

Premedication, by mouth

- **CHILD:** 1 month–18 years 500 micrograms/kg (max. 20 mg), 15–30 minutes before the procedure

Premedication, by intravenous injection

- **CHILD** 12–18 years: 25–50 micrograms/kg repeated as required (max. total dose 7.5 mg)

Induction (rarely used), by slow intravenous injection

- **ADULT:** 150–200 micrograms/kg (**ELDERLY** or **DEBILITATED:** 50–150 micrograms/kg), given in divided doses (max. 5 mg) at intervals of 2 minutes; maximum total dose 600 micrograms/kg
- **CHILD** 7–18 years: Initially 150 micrograms/kg (max. 7.5 mg) given in steps of 50 micrograms/kg (max. 2.5 mg) over 2–5 minutes; wait for 2–5 minutes then give additional doses of 50 micrograms/kg (max. 2.5 mg) every 2 minutes if necessary; max. total dose 500 micrograms/kg (not exceeding 25 mg)

Sedation of patients receiving intensive care

- *By slow intravenous injection*, initially 30–300 micrograms/kg given in steps of 1–2.5 mg every 2 minutes, then *by slow intravenous injection* or *by continuous intravenous infusion*, 30–200 micrograms/kg/hour; reduce dose (or reduce or omit initial dose) in hypovolemia, vasoconstriction, or hypothermia; lower doses may be adequate if opioid analgesic also used.

Sedation in intensive care by intravenous injection and continuous intravenous infusion

- **NEONATE** less than 32 weeks' gestational age: 30 micrograms/kg/hour *by continuous intravenous infusion* adjusted according to response
- **NEONATE** over 32 weeks' gestational age: 60 micrograms/kg/hour *by continuous intravenous infusion* adjusted according to response

- **CHILD** 1–6 months: 60 micrograms/kg/hour *by continuous intravenous infusion* adjusted according to response
- **CHILD** 6 months–12 years: Initially 50–200 micrograms/ kg *by slow intravenous injection* over at least 3 minutes followed by 30–120 micrograms/kg/hour *by continuous intravenous infusion*, adjusted according to response
- **CHILD** 12–18 years: Initially 30–300 micrograms/kg *by slow intravenous injection* given in steps of 1–2.5 mg every 2 minutes followed by 30–200 micrograms/kg/hour *by continuous intravenous infusion*, adjusted according to response

- **Adverse effects**

- Gastrointestinal disturbances, increased appetite, jaundice
- Hypotension, cardiac arrest, heart rate changes, anaphylaxis, thrombosis
- Laryngospasm, bronchospasm, respiratory depression, respiratory arrest (particularly with high doses or on rapid injection)
- Drowsiness, confusion, ataxia, amnesia, headache, euphoria, hallucinations, convulsions (more common in neonates), dizziness, vertigo, involuntary movements, paradoxical excitement and aggression (especially in children and elderly), dysarthria
- Urinary retention, incontinence, changes in libido
- Blood disorders
- Muscle weakness
- Visual disturbances
- Salivation changes
- Skin reactions
- Injection-site reactions

- **Morphine**

- **Dosage form**

- Injection: 10 mg/ml (sulfate or hydrochloride) in 1 ml ampoule. *See Section 2.2.*

- **Pethidine**

- **Dosage form**

- Oral ingestion tablets 50 mg and 100 mg
 - Injection 50 mg/ml ampoule (as hydrochloride). *See Section 2.2.*

- **Promethazine**

- **Dosage form**

- Oral liquid: 5 mg (hydrochloride)/5 ml

- **Uses**

- Premedication prior to surgery; anti-emetic (Section 17.2)

- **Contraindications**

- Child under 1 year
 - Impaired consciousness due to cerebral depressants or of other origin
 - Porphyria

- **Precautions**

- Prostatic hypertrophy, urinary retention
 - Glaucoma
 - Epilepsy
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Breast-feeding: Appendix C
 - Pregnancy: Appendix B
 - **Interactions:** Appendix A
 - **Skilled tasks:** Warn patient not to perform skilled tasks (for example, operating machinery or driving) for 24 hours.

- **Dose**

Premedication, by mouth, 1 hour before surgery

- **CHILD** over 1 year: 0.5–1 mg/kg

- **Adverse effects**

- Drowsiness (rarely paradoxical stimulation in children)
- Headache
- Anticholinergic effects such as dry mouth, blurred vision, and urinary retention

SECTION 2: Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIMs), medicines used to treat gout, and disease-modifying agents in rheumatoid disorders (DMARDs)

Drug treatment aims to modify the peripheral and central mechanisms involved in the development of pain. Neuropathic pain may respond only partially to conventional analgesics; treatment can be difficult and includes the use of carbamazepine for trigeminal neuralgia and amitriptyline for diabetic neuropathy and post-herpetic neuralgia. Pain may be modified by psychological factors and attention to these is essential in pain management.

Non-opioid analgesics are particularly suitable for musculoskeletal pain, whereas the opioid analgesics are more suitable for moderate-to-severe visceral pain. Non-opioid analgesics that also have anti-inflammatory actions include salicylates and other non-steroidal anti-inflammatory medicines (NSAIMs); they can reduce both pain and inflammation of chronic inflammatory disorders such as rheumatoid arthritis, but they do not alter or modify the disease process itself. For the management of rheumatoid arthritis, disease-modifying anti-rheumatic drugs (DMARDs) may favorably influence the disease process. The pain and inflammation of an acute attack of gout is treated with an NSAIM or colchicine; a xanthine oxidase inhibitor is used for long-term control of gout.

LML strengths and dosage forms are marked in *italic* with an asterisk.

2.1 Non-opioids and non-steroidal anti-inflammatory medicines

Non-opioid analgesics with anti-inflammatory activity include the salicylates (such as acetylsalicylic acid) and other NSAIMs (such as ibuprofen). Non-opioid analgesics with little or no anti-inflammatory activity include paracetamol.

Acetylsalicylic acid / aspirin

The principal effects of **acetylsalicylic acid** are anti-inflammatory, analgesic, antipyretic, and antiplatelet. Oral doses are absorbed rapidly from the gastrointestinal tract; rectal absorption is less reliable but suppositories are useful in patients unable to take oral dosage forms.

Acetylsalicylic acid is used for the management of mild-to-moderate pain, such as headache, acute migraine attacks, transient musculoskeletal pain, and dysmenorrhea, and for reducing fever. Although acetylsalicylic acid may be used in higher doses in the management of pain and inflammation of rheumatoid arthritis, other NSAIDs are preferred because they are likely to be better tolerated. Acetylsalicylic acid is also used for its antiplatelet properties. Adverse effects with analgesic doses are generally mild but include a high incidence of gastrointestinal irritation with slight blood loss, bronchospasm and skin reactions in hypersensitive patients, and increased bleeding time. Anti-inflammatory doses are associated with a much higher incidence of adverse reactions, and they also cause mild chronic salicylism, which is characterized by tinnitus and deafness.

Acetylsalicylic acid should be avoided in children under 16 years, unless specifically indicated (for example, in juvenile arthritis), because of an association with Reye syndrome (encephalopathy and liver damage); it should particularly be avoided during fever or viral infection in children and adolescents.

Paracetamol

Paracetamol is similar in analgesic and antipyretic efficacy to acetylsalicylic acid. It is used for mild-to-moderate pain, including headache and acute migraine attacks, and for reducing fever, including post-immunization pyrexia. Paracetamol is particularly useful in patients in whom salicylates or other NSAIDs are contraindicated, such as asthmatics and those with a history of peptic ulcer, or for children under the age of 16 years, in whom salicylates should be avoided because of the risk of Reye syndrome. It is generally preferred to acetylsalicylic acid, particularly in the elderly, because it is less irritating to the stomach. Unlike acetylsalicylic acid and other NSAIDs, paracetamol has little anti-inflammatory activity, which limits its usefulness for long-term treatment of pain associated with inflammation; however, it is useful in the management of osteoarthritis, a condition with only a small inflammatory component. In normal doses, adverse effects are rare, but overdosage with a single dose of 10–15 g is particularly dangerous because it may cause hepatocellular necrosis and, less frequently, renal tubular necrosis.

Non-steroidal anti-inflammatory medicines

NSAIDs, including **ibuprofen**, have analgesic, anti-inflammatory, and antipyretic properties.

In single doses, NSAIDs have analgesic activity comparable to that of paracetamol. In regular full dosage, they have a lasting analgesic and anti-inflammatory effect, which makes them useful for the management of continuous or regular pain due to inflammation.

Differences in anti-inflammatory activity between different NSAIDs are small, but there is considerable variation in individual patient response and in the incidence and type of adverse effects. Ibuprofen has fewer adverse effects than other NSAIDs, but its anti-inflammatory properties are weaker. Diclofenac and naproxen combine moderately potent anti-inflammatory activity with a relatively low incidence of adverse effects (but incidence is higher than that for ibuprofen).

Ibuprofen is used in the treatment of mild-to-moderate pain and in the management of pain and inflammation in rheumatoid arthritis and juvenile arthritis. It may also be of value in the less well-defined conditions of back pain and soft-tissue disorders. Ibuprofen is also used to reduce pain in children. **With all NSAIDs, caution should be exercised in the treatment of the elderly, in allergic disorders, and during pregnancy and breast-feeding.** In patients with renal, cardiac, or hepatic impairment, the dose should be kept as low as possible and renal function should be monitored. NSAIDs should not be given to patients with active peptic ulceration and should preferably not be used in those with a history of the disease. The most common adverse effects are generally gastrointestinal, including nausea, vomiting, diarrhea, and dyspepsia; hypersensitivity reactions including anaphylaxis, bronchospasm, and rash have been reported, as has fluid retention.

- **Acetylsalicylic acid**

- **Dosage form**

- Tablet: 75 mg,* 100 mg, 300 mg, 325 mg, and 500 mg

- **Uses**

- Mild-to-moderate pain, including dysmenorrhea, and headache
 - Pain and inflammation in rheumatic disease and other musculoskeletal disorders, including juvenile arthritis

- Pyrexia
- Acute migraine attack: Section 7.1
- Antiplatelet: Section 12.5
- **Contraindications**
 - Hypersensitivity (including asthma, angioedema, urticaria, or rhinitis) to acetylsalicylic acid or any other NSAID
 - Children and adolescents under 16 years (to reduce risk of Reye syndrome, *see also* introductory notes above)
 - Previous or active peptic ulceration
 - Hemophilia and other bleeding disorders
 - Not for treatment of gout
- **Precautions**
 - Asthma, allergic disease
 - Elderly
 - G6PD-deficiency
 - Dehydration
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Breast-feeding: Appendix C
 - Pregnancy: Appendix B
 - **Interactions:** Appendix A
- **Dose**

Mild-to-moderate pain, pyrexia, by mouth, with or after food

- **ADULT:** 300–900 mg every 4–6 hours if necessary; maximum, 4 g daily
- **CHILD** under 16 years: Not recommended

Inflammatory arthritis, by mouth, with or after food

- **ADULT:** 4–8 g daily in divided doses in acute conditions; up to 5.4 g daily may be sufficient in chronic conditions

Juvenile arthritis, by mouth with or after food

- **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

- **Adverse effects**

- Generally mild and infrequent for lower doses, but common with anti-inflammatory doses
- Gastrointestinal discomfort or nausea, ulceration with occult bleeding (occasionally major hemorrhage); also other hemorrhage including subconjunctival
- Hearing disturbances such as tinnitus (rarely deafness), vertigo, confusion
- Hypersensitivity reactions including angioedema, bronchospasm, rash
- Increased bleeding time
- Rarely edema, myocarditis, blood disorders (particularly thrombocytopenia)

- **Diclofenac**

- **Dosage form**

- Tablet: 25 mg, 50 mg, 75 mg, and 100 mg
- Injection: 25 mg/ml in 3 ml ampoule and 75 mg/3 ml ampoule
- Topical cream: 1% and 2% (as sodium or potassium salts)

- **Uses**

- Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders
- Acute gout
- Postoperative pain

- **Contraindications**

- Patients with a history of hypersensitivity to aspirin or any other NSAID, which includes those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID, and in coagulation defects

- Long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.
- Caution is also required in patients with connective-tissue disorders.
- Avoid suppositories in proctitis
- Avoid injections containing benzyl alcohol in neonates.
- **Intravenous use:** Additional contraindications include concomitant NSAID or anticoagulant use (including low-dose heparins), history of hemorrhagic diathesis, history of confirmed or suspected cerebrovascular bleeding, operations with high risk of hemorrhage, history of asthma, moderate or severe renal impairment (*see also* renal impairment under Precautions below), hypovolemia, dehydration.

○ **Precautions**

- NSAIDs should be used with caution in the elderly (risk of serious adverse effects and fatalities) and in coagulation defects.
- Bleeding associated with aspirin and other NSAIDs is more common in the elderly, who are more likely to have a fatal or serious outcome.
- NSAIDs are also a special hazard in patients with cardiac disease or renal impairment, which may again place older patients at particular risk.
- Caution is also required in patients with connective tissue disorders (*see* Adverse effects below).
- In patients with cardiac impairment, caution is required since NSAIDs may impair renal function (*see also* Adverse effects below).
- The selective inhibitors of cyclo-oxygenase-2 should be used with caution in patients with a history of cardiac failure, left ventricular dysfunction, hypertension, in patients with edema for any other reason, and patients with risk factors for cardiovascular events.
- Nonselective NSAIDs should be used with caution in uncontrolled hypertension, heart failure, ischemic heart disease, peripheral artery disease, cerebrovascular disease, and when used long-term in patients with risk factors for cardiovascular events.
- NSAIDs should also be used with caution in Crohn's disease or ulcerative colitis, as these conditions may be exacerbated, and also avoided in acute porphyria.

- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B

○ **Dose**

By mouth

- 75–150 mg daily in 2–3 divided doses. Total maximum daily dose should not exceed 150 mg.

Juvenile idiopathic arthritis

- **CHILD** 6 months–18 years: *By mouth*, 1.5–2.5 mg/kg (max. 75 mg) twice daily. Total daily dose may alternatively be given in 3 divided doses.

Dose by deep intramuscular injection into the gluteal muscle, acute exacerbations of pain and postoperative pain

- 75 mg once daily (twice daily in severe cases) for maximum 2 days

Ureteric colic

- 75 mg then a further 75 mg after 30 minutes if necessary

○ **Adverse effects**

- Gastrointestinal disturbances including discomfort, nausea, diarrhea, and occasionally bleeding and ulceration occur.
- Systemic as well as local effects of NSAIDs contribute to gastrointestinal damage.
- Taking oral formulations with milk or food, or using enteric-coated formulations, or changing the route of administration, may only partially reduce symptoms such as dyspepsia.
- Other side effects include hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm), headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, hearing disturbances such as tinnitus, photosensitivity, and hematuria.

- Blood disorders have also occurred.
- Fluid retention may occur (rarely precipitating congestive heart failure); blood pressure may be raised.
- Renal failure may be provoked by NSAIDs, especially in patients with preexisting renal impairment.
- Rarely, papillary necrosis or interstitial fibrosis associated with NSAIDs can lead to renal failure.
- Hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other rare side effects.
- Induction of or exacerbation of colitis or Crohn's disease has been reported.
- Aseptic meningitis has been reported rarely with NSAIDs; patients with connective tissue disorders such as systemic lupus erythematosus may be especially susceptible.

- **Ibuprofen**

Ibuprofen is a representative NSAID and various medicines of this group can be used as alternative.

- **Dosage form**

- Tablet: 200 mg, 400 mg, and 600 mg
- Topical ointment: 10% in 30 g tube
- Oral syrup: 100 mg/5 ml in 60 ml

- **Uses**

- Pain and inflammation in rheumatic disease and other musculoskeletal disorders including juvenile arthritis
- Mild-to-moderate pain including dysmenorrhea and headache
- Pain and fever
- Acute migraine attack

- **Contraindications**

- Hypersensitivity (including asthma, angioedema, urticaria, or rhinitis) to acetylsalicylic acid or any other NSAID
- Active peptic ulceration
- **Precautions**
 - Cardiac disease
 - Elderly
 - Coagulation defects
 - Allergic disorders
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Breast-feeding: Appendix C
 - Pregnancy: Appendix B
 - **Interactions:** Appendix A
 - **Topical ointment:** Avoid contact with eyes, mucous membranes, inflamed and broken skin. In case of development of rashes stop the treatment. Wash hands after use and avoid use in close bandages. Application of the gel over a large area of the skin may cause hypersensitivity, asthma, and renal function disturbance. **Not suitable for children and use with caution in pregnancy and breast-feeding.**

○ **Dose**

Mild-to-moderate pain, pyrexia, inflammatory musculoskeletal disorders, by mouth with or after food

- **ADULT:** 1.2–1.8 g daily in 3–4 divided doses, increased 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

Juvenile arthritis, by mouth with or after food

- **CHILD** over 7 kg: 30–40 mg/kg daily in 3–4 divided doses

Pain in CHILD (not recommended for children under 7 kg), by mouth with or after food

- **CHILD:** 20–40 mg/kg daily in divided doses
or
- **CHILD** 1–2 years: 50 mg 3–4 times daily
- **CHILD** 3–7 years: 100 mg 3–4 times daily
- **CHILD** 8–12 years: 200 mg 3–4 times daily

Topical ointment

- For the management of musculoskeletal pain, 3–4 times daily for 14 days.
Revise treatment after 14 days.

○ **Adverse effects**

- Gastrointestinal disturbances including nausea, diarrhea, dyspepsia, ulceration, and hemorrhage
- Hypersensitivity reactions including rash, angioedema, and bronchospasm
- Headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, tinnitus, photosensitivity, and hematuria
- Fluid retention (rarely precipitating congestive heart failure in the elderly), raised blood pressure, and renal failure
- Rarely hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (Stevens-Johnson syndrome), toxic dermal necrolysis (Lyell syndrome), colitis, and aseptic meningitis
- **Topical ointment** may cause hypersensitivity reaction: asthma and photosensitivity (avoid exposure to sunlight).

• **Paracetamol**

○ **Dosage form**

- Oral liquid: 120 mg/5 ml and 250 mg/5 ml
- Tablet: 100 mg, 325 mg, and 500 mg
- Oral ingestion drop: 100 mg/ml
- Suppository rectal: 125 mg
- Infusion solution: 10 mg/ml in 100 ml vial
- Injection ampoule: 225 mg/3 ml

- **Uses**

- Mild-to-moderate pain including dysmenorrhea and headache
- Pain relief in osteoarthritis and soft tissue lesions
- Pyrexia including post-immunization pyrexia
- Acute migraine attack: Section 7.1

- **Precautions**

- Alcohol dependence
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B
- **Interactions:** Appendix A

- **Dose**

Post-immunization pyrexia, by mouth

- **INFANT** 2–3 months: 60 mg followed by a second dose, if necessary, 4–6 hours later. Warn parents to seek medical advice if pyrexia persists after second dose.

Mild-to-moderate pain, pyrexia, by mouth

- **ADULT:** 0.5–1 g every 4–6 hours, maximum 4 g daily
- **CHILD** under 3 months: See Note below.
- **CHILD** 3 months–1 year: 60–125 mg
- **CHILD** 1–5 years: 120–250 mg
- **CHILD** 6–12 years: 250–500 mg (in children, doses may be repeated every 4–6 hours if necessary. Maximum: 4 doses in 24 hours.

Mild-to-moderate pain, pyrexia, by rectum

- **ADULT:** 0.5–1 g
- **CHILD** 1–5 years: 125–250 mg

- **CHILD** 6–12 years: 250–500 mg (doses may be inserted every 4–6 hours if necessary); maximum: 4 doses in 24 hours

Note: Infants under 3 months should not be given paracetamol unless advised by a doctor; in that case, a dose of 10 mg/kg (5 mg/kg if jaundiced) is suitable.

- **Adverse effects**

- Rare but rash and blood disorders reported
- **Important:** Liver damage (and less frequently renal damage) following overdosage.

2.2 Opioid analgesics

Morphine is effective in relieving moderate-to-severe pain, particularly of visceral origin; there is a large variation in patient response. Weaker opioids such as codeine are suitable for mild-to-moderate pain.

Codeine is an opioid analgesic much less potent than morphine and much less liable, in normal doses, to produce adverse effects, including dependency. It is effective for mild-to-moderate pain but is too constipating for long-term use.

Morphine remains the most valuable analgesic for severe pain. In addition to pain relief, it confers a state of euphoria and mental detachment; repeated administration may cause dependence and tolerance, but this should not be a deterrent in the control of pain in terminal illness.

Regular use may also be appropriate for certain cases of non-malignant pain, but specialist supervision is required. In usual doses, common adverse effects include nausea, vomiting, constipation, and drowsiness; larger doses produce respiratory depression and hypotension.

Morphine is given by mouth as an oral solution, immediate-release tablet, or sustained-release tablet for chronic pain treatment. Pain should be controlled using immediate-release preparations first. The total morphine requirement over 24 hours can then be established and

the daily dose may be given as a sustained-release preparation (designed for twice-daily administration) every 12 hours.

Additional doses of morphine can be given for breakthrough pain every 4 hours if necessary, using immediate-release morphine tablets or oral solution; the dose should be about one-sixth of the total daily dose of oral morphine. The regular dose should then be reviewed and adjusted according to the need for additional doses; increments should be made to the dose, rather than to the frequency of administration.

Opioid analgesic overdose

Opioids cause coma, respiratory depression, and pinpoint pupils. **Naloxone** is a specific antidote indicated if there is coma or bradypnea. Naloxone has a shorter duration of action than many opioids, so close monitoring and repeated injections are required depending on respiratory rate and depth of coma; alternatively, naloxone may be given by continuous intravenous infusion and the rate of infusion adjusted according to vital signs. The effects of some opioids such as buprenorphine (Section 25.5) are only partially reversed by naloxone.

Methadone (Section 25.5) has a very long duration of action and patients may need to be monitored for long periods after large overdoses. Multiple doses of naloxone may be required after overdoses of sustained-release opioid preparations (including modified-release morphine sulfate tablets).

Acute withdrawal syndromes may be precipitated by the use of naloxone in patients with a physical dependence on opioids or in overdose with large doses; a withdrawal syndrome may occur in neonates of opioid-dependent mothers.

- **Morphine**

- **Dosage form**

- Injection: 10 mg/ml (morphine hydrochloride or morphine sulfate) in 1 ml ampoule

- **Uses**

- Severe pain (acute and chronic)

- Myocardial infarction, acute pulmonary edema
- Adjunct during major surgery and postoperative analgesia
- **Contraindications**
 - Avoid in acute respiratory depression, acute alcoholism, and where risk of paralytic ileus exists.
 - Also avoid in raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment).
 - Avoid injection in pheochromocytoma.
- **Precautions**
 - Reduce dose or avoid in elderly and debilitated patients
 - Dependence (severe withdrawal symptoms can develop if withdrawn abruptly)
 - Hypothyroidism
 - Convulsive disorders
 - Decreased respiratory reserve and acute asthma
 - Hypotension
 - Prostatic hypertrophy
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Breast-feeding: Appendix C
 - Pregnancy: Appendix B
 - **Interactions:** Appendix A
- **Dose**

Acute pain, by subcutaneous injection (not suitable for edematous patients) or by intramuscular injection

- **ADULT:** 10 mg every 4 hours if necessary (15 mg for heavier, well-muscled patients)
- **INFANT** up to 1 month: 150 micrograms/kg; 1–12 months, 200 micrograms/kg
- **CHILD** 1–5 years: 2.5–5 mg; 6–12 years, 5–10 mg

Chronic pain, by subcutaneous injection (not suitable for edematous patients) or by intramuscular injection

- **ADULT:** 5–20 mg regularly every 4 hours; dose may be increased according to need

Myocardial infarction, by slow intravenous injection (2 mg/min)

- **ADULT:** 10 mg followed by a further 5–10 mg if necessary; **ELDERLY** or **DEBILITATED** patients, reduce dose by one-half

Acute pulmonary edema, by slow intravenous injection (2 mg/min)

- **ADULT:** 5–10 mg

Note: The doses stated above refer equally to morphine sulfate and morphine hydrochloride.

- **Adverse effects**

- Nausea, vomiting (particularly in initial stages), constipation
- Drowsiness
- Also dry mouth, anorexia, spasm of urinary and biliary tract
- Bradycardia, tachycardia, palpitation, euphoria, decreased libido, rash, urticaria, pruritus, sweating, headache, facial flushing, vertigo, postural hypotension, hypothermia, hallucinations, confusion, dependence, miosis
- Larger doses produce respiratory depression, hypotension, and muscle rigidity.

- **Pethidine**

- **Dosage form**

- Tablet: 50 mg and 100 mg
- Injection: 50 mg/ml in 1 and 2 ml ampoules (as hydrochloride)

- **Uses**

- Moderate-to-severe pain, obstetric analgesia
- Perioperative analgesia

- **Contraindications**

- Opioid analgesics should be avoided in patients with acute respiratory depression and when there is a risk of paralytic ileus.
- They are also contraindicated in conditions associated with raised intracranial pressure and in head injury (opioid analgesics interfere with pupillary responses vital for neurological assessment).
- Comatose patients should not be treated with opioid analgesics.
- Pheochromocytoma

- **Precautions**

- Opioids should be used with caution in patients with impaired respiratory function (avoid in chronic obstructive pulmonary disease) and asthma (avoid during an acute attack), hypotension, shock, myasthenia gravis, prostatic hypertrophy, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders.
- A reduced dose is recommended in elderly or debilitated patients, in hypothyroidism, and in adrenocortical insufficiency.
- Repeated use of opioid analgesics is associated with the development of psychological and physical dependence; although this is rarely a problem with therapeutic use, caution is advised if prescribing for patients with a history of drug dependence.
- Avoid abrupt withdrawal after long-term treatment.
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B

- **Dose**

Acute pain, by mouth

- **ADULT:** 50–150 mg every 4 hours
- **CHILD:** 0.5–2 mg/kg

Acute pain, by subcutaneous or intramuscular injection

- **ADULT:** 25–100 mg (**ELDERLY** or **DEBILITATED**, initially 25 mg), repeated after 4 hours
- **CHILD,** by intramuscular injection: 0.5–2 mg/kg.

Acute pain, by slow intravenous injection

- **ADULT:** 25–50 mg (**ELDERLY** or **DEBILITATED**, initially 25 mg), repeated after 4 hours

Obstetric analgesia, by subcutaneous or intramuscular injection

- **ADULT:** 50–100 mg, repeated 1–3 hours later if necessary; maximum 400 mg in 24 hours.

Premedication: by intramuscular injection

- **ADULT:** 25–100 mg 1 hour before operation (**ELDERLY** or **DEBILITATED**, 25 mg)
- **CHILD:** 0.5–2 mg/kg

Postoperative pain, by subcutaneous or intramuscular injection

- **ADULT:** 25–100 mg (**ELDERLY** or **DEBILITATED**, initially 25 mg), every 2–3 hours if necessary
- **CHILD,** by intramuscular injection: 0.5–2 mg/kg

Note: In the postoperative period, the patient should be closely monitored for pain relief as well as for side effects, especially respiratory depression.

○ **Adverse effects**

- Opioid analgesics share many side effects, although qualitative and quantitative differences exist. The most common side effects include nausea and vomiting (particularly in initial stages), constipation, dry mouth, and biliary spasm
- Larger doses produce muscle rigidity, hypotension, and respiratory depression.
- Other common side effects of opioid analgesics include bradycardia, tachycardia, palpitation, edema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, mood changes, dependence, dizziness, confusion,

drowsiness, sleep disturbances, headache, sexual dysfunction, difficulty with micturition, urinary retention, ureteric spasm, miosis, visual disturbances, sweating, flushing, rash, urticaria, and pruritus.

- Restlessness
- Tremor and hypothermia
- Convulsions reported in overdosage
- Long-term use of opioid analgesics can cause hypogonadism and adrenal insufficiency in both men and women. This can lead to amenorrhea, reduced libido, infertility, depression, and erectile dysfunction.
- Long-term use of opioid analgesics has been associated with a state of abnormal pain sensitivity (hyperalgesia). Pain associated with hyperalgesia is usually qualitatively distinct from pain associated with disease progression or breakthrough pain, and is often more diffuse and less defined. Treatment of hyperalgesia involves reducing the dose of opioid medication or switching therapy; cases of suspected hyperalgesia should be referred to a specialist pain team.

- **Tramadol**

- **Dosage form**

- Oral ingestion capsules: 50 mg and 100 mg
 - Injection: 50 mg/ml in 2 ml ampoule (as hydrochloride)

- **Uses**

- Moderate-to-severe pain

- **Contraindications**

- Opioid analgesics should be avoided in patients with acute respiratory depression and when there is a risk of paralytic ileus.
 - They are also contraindicated in conditions associated with raised intracranial pressure and in head injury (opioid analgesics interfere with pupillary responses vital for neurological assessment).
 - Comatose patients should not be treated with opioid analgesics.
 - Uncontrolled epilepsy

- **Precautions**

- Opioids should be used with caution in patients with impaired respiratory function (avoid in chronic obstructive pulmonary disease) and asthma (avoid during an acute attack), hypotension, shock, myasthenia gravis, prostatic hypertrophy, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders.
- A reduced dose is recommended in elderly or debilitated patients, in hypothyroidism, and in adrenocortical insufficiency.
- Repeated use of opioid analgesics is associated with the development of psychological and physical dependence; although this is rarely a problem with therapeutic use, caution is advised if prescribing for patients with a history of drug dependence.
- Avoid abrupt withdrawal after long-term treatment
- Impaired consciousness
- Excessive bronchial secretions
- Not suitable as a substitute in opioid-dependent patients
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B

- **Dose**

- By mouth*

- **ADULT** and **CHILD** over 12 years: 50–100 mg, not more often than every 4 hours
 - Total of more than 400 mg daily not usually required

- By intramuscular injection or by intravenous injection (over 2–3 minutes) or by intravenous infusion*

- **ADULT** and **CHILD** over 12 years: 5–100 mg every 4–6 hours

- Postoperative pain*

- 100 mg initially, then 50 mg every 10–20 minutes if necessary during first hour to total maximum 250 mg (including initial dose) in first hour, then 50–100 mg every 4–6 hours; maximum 600 mg daily

○ **Adverse effects**

- Opioid analgesics share many side effects, although qualitative and quantitative differences exist. The most common side effects include nausea and vomiting (particularly in initial stages), constipation, dry mouth, and biliary spasm; larger doses produce muscle rigidity, hypotension, and respiratory depression.
- Other common side effects of opioid analgesics include bradycardia, tachycardia, palpitation, edema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, mood changes, dependence, dizziness, confusion, drowsiness, sleep disturbances, headache, sexual dysfunction, difficulty with micturition, urinary retention, ureteric spasm, miosis, visual disturbances, sweating, flushing, rash, urticaria, and pruritus.
- Long-term use of opioid analgesics can cause hypogonadism and adrenal insufficiency in both men and women. This can lead to amenorrhea, reduced libido, infertility, depression, and erectile dysfunction.
- Long-term use of opioid analgesics has been associated with a state of abnormal pain sensitivity (hyperalgesia). Pain associated with hyperalgesia is usually qualitatively distinct from pain associated with disease progression or breakthrough pain, and is often more diffuse and less defined. Treatment of hyperalgesia involves reducing the dose of opioid medication or switching therapy; cases of suspected hyperalgesia should be referred to a specialist pain team.
- Also diarrhea, fatigue
- Less commonly retching, gastritis, flatulence
- Rarely anorexia, syncope, hypertension, bronchospasm, dyspnea, wheezing, seizures, paresthesia, muscle weakness
- Blood disorders also reported

2.3 Medicines used to treat gout

Acute gout

Acute attacks of gout are usually treated with high doses of an NSAID such as **indomethacin** (150–200 mg daily in divided doses); ibuprofen has weaker anti-inflammatory properties than other NSAIDs and is therefore less suitable for treatment of gout. Salicylates, including acetylsalicylic acid are also not suitable because they may increase plasma urate concentrations. Colchicine is an alternative for those patients in whom NSAIDs are contraindicated. Its use is limited by toxicity with high doses. It does not induce fluid retention and can therefore be given to patients with heart failure; it can also be given to patients receiving anticoagulants.

Chronic gout

For long-term control of gout in patients who have frequent acute attacks, the presence of tophi, or chronic gouty arthritis, the xanthine oxidase inhibitor **allopurinol** may be used to reduce production of uric acid. Treatment for chronic gout should not be started until after an acute attack has completely subsided, usually 2–3 weeks. The initiation of allopurinol treatment may precipitate an acute attack and therefore a suitable NSAID or colchicine should be used as a prophylactic and continued for at least 1 month after the hyperuricemia has been corrected. If an acute attack develops during treatment for chronic gout, then allopurinol should continue at the same dosage and the acute attack should be treated in its own right. Treatment for chronic gout should be continued indefinitely to prevent further attacks of gout.

- **Allopurinol**

- **Dosage form**

- Tablets: 100 mg and 300 mg

- **Uses**

- Prophylaxis of gout
 - Prophylaxis of hyperuricemia associated with cancer chemotherapy

- **Contraindications**

- Acute gout (if an acute attack occurs while receiving allopurinol, continue prophylaxis and treat attack separately)

- **Precautions**

- Ensure adequate fluid intake of 2–3 L daily.
- Withdraw treatment if rash occurs, reintroduce if rash is mild, but discontinue immediately if it recurs.
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B
- **Interactions:** Appendix A

- **Dose**

Prophylaxis of gout, by mouth

- **ADULT:** Initially 100 mg daily as a single dose, preferably after food, then adjusted according to plasma or urinary uric acid concentration (usual maintenance dose in mild conditions, 100–200 mg daily; in moderately severe conditions, 300–600 mg daily; in severe conditions; 700–900 mg daily; doses over 300 mg daily given in divided doses)

Note: Initiate 2–3 weeks after acute attack has subsided and administer a suitable NSAID (not ibuprofen or a salicylate) or colchicine from the start of allopurinol treatment and continue for at least 1 month after correction of hyperuricemia.

Prophylaxis of hyperuricemia in cancer patients undergoing chemotherapy, by mouth

- **ADULT:** Maintenance doses as for acute gout, adjusted according to response, commencing 24 hours before chemotherapy treatment and continuing for 7–10 days afterward
- **CHILD** under 15 years: 10–20 mg/kg daily (max. 400 mg daily)

- **Adverse effects**

- Rash (see Precautions above)

- Hypersensitivity reactions occur rarely and include fever, lymphadenopathy, arthralgia, eosinophilia, erythema multiforme (Stevens-Johnson syndrome) or toxic epidermal necrolysis, vasculitis, hepatitis, renal impairment and, very rarely, seizures.
- Gastrointestinal disorders
- Rarely malaise, headache, vertigo, drowsiness, visual and taste disturbances, hypertension, alopecia, hepatotoxicity, paresthesia, neuropathy, gynecomastia, and blood disorders (including leukopenia, thrombocytopenia, hemolytic anemia, and aplastic anemia)

- **Colchicine**

- **Dosage form**

- Tablet: 500 micrograms

- **Uses**

- Acute gout
- Short-term prophylaxis during initial therapy with allopurinol and uricosuric drugs

- **Contraindications**

- Blood disorders
- Avoid in pregnancy (teratogenicity in animal studies)

- **Precautions**

- The use of colchicine is limited by the development of toxicity at higher doses, but it is of value in patients with heart failure; also the elderly.
- Gastrointestinal disease
- Cardiac disease
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B
- **Interactions:** Appendix A

- **Dose**

- Acute gout*

- Acute gout, 500 micrograms 2–4 times daily until symptoms relieved, maximum 6 mg per course; course not to be repeated within 3 days

- Prevention of gout attacks during initial treatment with allopurinol or uricosuric drugs*

- 500 micrograms twice daily

- **Adverse effects**

- Nausea, vomiting, and abdominal pain. Excessive doses may cause profuse diarrhea, gastrointestinal hemorrhage, rash, renal and hepatic damage.
 - Rarely peripheral neuritis, inhibition of spermatogenesis, myopathy, alopecia, and with prolonged-treatment blood disorders

2.4 Disease-modifying agents used in rheumatoid disorders

The process of cartilage and bone destruction that occurs in rheumatoid arthritis may be reduced by use of a diverse group of medicines known as DMARDs (disease-modifying anti-rheumatic drugs). DMARDs include chloroquine, penicillamine, sulfasalazine, and the immunosuppressants azathioprine and methotrexate. Treatment should be started early in the course of the disease, before joint damage starts. Treatment is usually initiated with an NSAID when the diagnosis is uncertain and the disease course unpredictable. However, when the diagnosis, progression, and severity of rheumatic disease have been confirmed, a DMARD should be introduced.

DMARDs do not produce an immediate improvement but require 4–6 months of treatment for a full response. Their long-term use is limited by toxicity and loss of efficacy. If one drug does not lead to objective benefit within 6 months, it should be discontinued and another DMARD substituted. Adverse reactions with DMARDs occur frequently and may be life-threatening; careful monitoring is needed to avoid severe toxicity. Blood disorders (bone

marrow suppression) can occur during treatment with many DMARDs; blood counts should be carried out before and during treatment, and patients should be advised to report without delay any unexplained symptom such as bleeding, bruising, purpura, infection, sore throat, or fever. It has been suggested that combinations of DMARDs may be more effective than single drugs, but increased toxicity may be a problem; whether used alone or in combination, they should be prescribed only by specialists to ensure that they are used safely and to best advantage.

Sulfasalazine has a beneficial anti-inflammatory effect and is considered by some rheumatologists to be a first-line DMARD, but it is poorly tolerated by about 25% of patients. Adverse reactions include blood disorders, hepatotoxicity, skin reactions, and gastrointestinal disturbances.

Methotrexate, an immunosuppressant, is considered to be a first-line DMARD; at the low doses used for rheumatoid arthritis, it is well tolerated but there remains the risk of blood disorders and of hepatic and pulmonary toxicity. Other immunosuppressant drugs, including **azathioprine**, are generally reserved for use in patients with severe disease who have failed to respond to other DMARDs, especially those with extracellular manifestations such as vasculitis. Immunosuppressants are used in psoriatic arthritis. Adverse reactions include blood disorders, alopecia, nausea, and vomiting.

The antimalarial **chloroquine** is less effective than most other DMARDs, but as it is generally better tolerated it may be preferred in the treatment of mild rheumatoid arthritis. Chloroquine should not be used for psoriatic arthritis. Because long-term therapy can result in retinopathy, ophthalmological examinations should be conducted before and during treatment.

Penicillamine is not a first-line drug, and its use is limited by significant adverse effects including blood disorders, proteinuria, and rash.

Corticosteroids are potent anti-inflammatory drugs, but their place in the treatment of rheumatoid arthritis remains controversial. Their usefulness is limited by adverse effects and their use should be controlled by specialists. Corticosteroids are usually reserved for use in

patients with severe disease that has failed to respond to other anti-rheumatic drugs, or where there are severe extra-articular effects such as vasculitis.

Corticosteroids are also used to control disease activity during initial therapy with DMARDs. Although corticosteroids are associated with bone loss, this appears to be dose-related; recent studies have suggested that a low dose of a corticosteroid started during the first 2 years of moderate-to-severe rheumatoid arthritis may reduce the rate of joint destruction. The smallest effective dose should be used, such as oral prednisolone 7.5 mg daily, for 2–4 years, and at the end of treatment the dose should be tapered off slowly to avoid possible long-term adverse effects. Relatively high doses of a corticosteroid, in combination with cyclophosphamide, may be needed to control vasculitis.

- **Chloroquine**

- **Dosage form**

- Tablet: 150 mg (base)
 - Oral syrup: 50 mg/5 ml

Note: Chloroquine base, 150 mg, is approximately equivalent to chloroquine sulfate, 200 mg, or chloroquine phosphate, 250 mg.

- **Uses**

- Rheumatoid arthritis (including juvenile arthritis)
 - Malaria (Section 6.5.3)

- **Contraindication**

- Psoriatic arthritis

- **Precautions**

- Monitor visual acuity throughout treatment and warn patient to report immediately any unexplained visual disturbances.
 - Neurological disorders including epilepsy
 - Severe gastrointestinal disorders

- G6PD deficiency
 - Elderly
 - May exacerbate psoriasis and aggravate myasthenia gravis
 - Porphyria
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Breast-feeding: Appendix C
 - Pregnancy: Appendix B
 - **Interactions:** Appendix A
- **Dose**
 - Administered on expert advice

Note: All doses are given in terms of chloroquine base.

Rheumatoid arthritis, by mouth

- **ADULT:** 150 mg daily; maximum 2.5 mg/kg daily
- **CHILD:** Up to 3 mg/kg daily

Note: To avoid excessive dosage in obese patients, the dose of chloroquine should be calculated on the basis of lean body weight.

- **Adverse effects**
 - Gastrointestinal disturbances, headache, skin reactions (including rash and pruritus)
 - Less frequently ECG changes, convulsions, visual changes, retinal damage, keratopathy, ototoxicity, hair depigmentation, alopecia, and discoloration of skin, nails, and mucous membranes
 - Rarely blood disorders (including thrombocytopenia, agranulocytosis, and aplastic anemia), mental changes (including emotional disturbances and psychosis), myopathy (including cardiomyopathy and neuromyopathy), acute generalized exanthematous pustulosis, exfoliative dermatitis, erythema multiforme (Stevens-Johnson syndrome), photosensitivity, and hepatic damage

- **Important:** Arrhythmias and convulsions in overdose

- **Methotrexate**

Methotrexate is a complementary medicine for rheumatoid arthritis.

- **Dosage form**

- Tablet: 2.5 mg (as sodium salt)

- **Uses**

- Rheumatoid arthritis
- Malignant disease (Section 8.2)

- **Contraindications**

- Pregnancy and breast-feeding
- Immunodeficiency syndromes
- Significant pleural effusion or ascites

- **Precautions**

- Monitor throughout treatment (including blood counts and hepatic and renal function tests).
- Reduce dose or withdraw if acute infection develops.
- Peptic ulceration, ulcerative colitis, diarrhea, ulcerative stomatitis
- Advise patient to avoid self-medication with salicylates or other NSAIDs.
- Warn patient with rheumatoid arthritis to report cough or dyspnea.
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B
- **Interactions:** Appendix A
- **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.

- **Dose**

- Administered on expert advice

Rheumatoid arthritis, by mouth

- **ADULT:** 7.5 mg once *weekly* (as a single dose or divided into 3 doses of 2.5 mg given at intervals of 12 hours), adjusted according to response; maximum total dose, 20 mg *weekly*.

Important: The doses are **weekly** doses and care is required to ensure that the correct dose is prescribed and dispensed.

- **Adverse effects**

- Blood disorders (bone marrow suppression), liver damage, pulmonary toxicity
- Gastrointestinal disturbances. If stomatitis and diarrhea occur, stop treatment.
- Renal failure
- Skin reactions, alopecia, osteoporosis, arthralgia, myalgia, ocular irritation
- Precipitation of diabetes

- **Penicillamine**

Penicillamine is a complementary medicine for rheumatoid arthritis.

- **Dosage form**

- Capsule or tablet: 125 mg and 250 mg

- **Uses**

- Severe rheumatoid arthritis
- Copper and lead poisoning (Section 4.2)

- **Contraindications**

- Lupus erythematosus

- **Precautions**

- Monitor throughout treatment (including blood counts and urine tests)
- Concomitant nephrotoxic drugs (increased risk of toxicity)
- Avoid concurrent gold, chloroquine, or immunosuppressive treatment.
- Avoid oral iron within 2 hours of a dose.
- Rarely patients hypersensitive to penicillin may react to penicillamine.
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- **Interactions:** Appendix A
- **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.

○ **Dose**

- Administered on expert advice

Rheumatoid arthritis, by mouth

- **ADULT:** Initially 125–250 mg daily before food for 1 month, increased by similar amounts at intervals of not less than 4 weeks to a usual maintenance dose of 500–750 mg daily in divided doses; maximum 1.5 g daily
- **ELDERLY:** Initially up to 125 mg daily before food for 1 month, increased at intervals of not less than 4 weeks; maximum, 1 g daily
- **CHILD** 8–12 years: Initially 2.5–5 mg/kg daily, gradually increased to a usual maintenance dose of 15–20 mg/kg daily at intervals of 4 weeks over a period of 3–6 months

○ **Adverse effects**

- Initially nausea (reduced if taken before food or on retiring, and if initial dose is increased gradually), anorexia, fever, and skin reactions
- Taste loss (mineral supplements not recommended)
- Blood disorders including thrombocytopenia, leukopenia, agranulocytosis, and aplastic anemia
- Proteinuria
- Rarely hematuria (withdraw immediately)

- Hemolytic anemia, nephrotic syndrome, lupus erythematosus–like syndrome, myasthenia-like syndrome, polymyositis (rarely with cardiac involvement), dermatomyositis, mouth ulcers, stomatitis, alopecia, bronchiolitis and pneumonitis, pemphigus
- Glomerulonephritis (Goodpasture syndrome) and erythema multiforme (Stevens-Johnson syndrome) also reported
- Male and female breast enlargement reported
- Rash (early rash disappears on withdrawal of treatment—reintroduce at a lower dose and increase gradually; late rash is more resistant—either reduce dose or withdraw treatment)

- **Sulfasalazine**

Sulfasalazine is a complementary medicine for rheumatoid arthritis.

- **Dosage form**

- Tablet: Enteric-coated 500 mg

- **Uses**

- Severe rheumatoid arthritis
- Ulcerative colitis and Crohn's disease (Section 17.3)

- **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
- History of allergy
- G6PD deficiency
- Slow acetylator status

- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B
- **Interactions:** Appendix A
- **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.

○ **Dose**

- Administered on expert advice

Rheumatoid arthritis, by mouth (as gastro-resistant tablets)

- **ADULT:** Initially 500 mg daily, increased by 500 mg at intervals of 1 week to a maximum of 2–3 g daily in divided doses

Juvenile idiopathic arthritis, by mouth

- **CHILD:** 2–18 years initially 5 mg/kg twice daily for 1 week, then 10 mg/kg twice daily for 1 week, then 20 mg/kg twice daily for 1 week, maintenance dose 20–25 mg/kg twice daily
- **CHILD** 2–12 years: Maximum 2 g daily
- **CHILD** 12–18 years: Maximum 3 g daily

○ **Adverse effects**

- Nausea, diarrhea, headache, loss of appetite
- Fever
- Blood disorders (including Heinz body anemia, megaloblastic anemia, leukopenia, neutropenia, and thrombocytopenia)
- Hypersensitivity reactions (including rash, urticaria, erythema multiforme [Stevens-Johnson syndrome], 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 edema)
- Stomatitis, parotitis
- Ataxia, aseptic meningitis, vertigo, tinnitus, alopecia, peripheral neuropathy, insomnia, depression, hallucinations
- Renal effects (including proteinuria, crystalluria, and hematuria)
- Oligospermia
- Rarely acute pancreatitis, hepatitis
- Urine may be colored orange
- Some soft contact lenses may be stained.

SECTION 3: Anti-allergics and medicines used in anaphylaxis

The H1-receptor antagonists are generally referred to as antihistamines. They inhibit the wheal, pruritus, sneezing, and nasal secretion responses that characterize allergy.

Antihistamines thus relieve the symptoms of allergic reactions, such as urticaria, allergic rhinitis, and allergic conjunctivitis; they also control pruritus in skin disorders, such as eczema. Antihistamines are used to treat drug allergies, food allergies, insect stings, and some of the symptoms of anaphylaxis and angioedema. Drug treatment and other supportive care should not be delayed in critically ill patients (see Allergic emergencies below). Specific precipitants should be sought and if identified, further exposure avoided and desensitization considered.

In practice, all antihistamines are equally effective in relieving the symptoms of allergic reactions and differ mainly in the intensity of their sedative and anticholinergic (or, more correctly, antimuscarinic) effects. Selection of an antihistamine should thus be based on the intended therapeutic use, the likely adverse reactions, and the cost. Drowsiness and sedation are particular disadvantages of the older antihistamines, such as **chlorphenamine**; patients should be warned against driving or operating machinery. Newer antihistamines do not cause significant sedation. Other central nervous system depressants, including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytics, and neuroleptics, may enhance the sedative effects of antihistamines. Since antihistamines interfere with skin tests for allergy, they should be stopped at least 1 week before such tests.

Corticosteroids, such as **dexamethasone**, **hydrocortisone**, and **prednisolone**, suppress or prevent almost all symptoms of inflammation associated with allergy. The route of administration depends on the particular type of allergic condition. For example, for a mild allergic skin reaction, the best therapy may be the use of a corticosteroid ointment or cream.

If the skin reaction does not respond to topical corticosteroid therapy, it may be necessary to give a corticosteroid orally.

Allergic reactions of limited duration and with mild symptoms, such as urticaria or allergic rhinitis, usually require no treatment. If, on the other hand, symptoms become persistent, antihistamines constitute the mainstay of treatment. However, oral corticosteroids may be required for a few days in an acute attack of urticaria or for severe skin reactions. Oral corticosteroids are also used to relieve severe exacerbations in chronic urticaria, but long-term use should be avoided.

Corticosteroids may be used topically to reduce inflammation in allergic rhinitis but should only be used systemically for this condition when symptoms are disabling.

Adverse effects associated with long-term use of corticosteroids include inhibition of growth in children, disturbances of electrolyte balance (leading to edema, hypertension, and hypokalemia), osteoporosis, spontaneous fractures, skin thinning, increased susceptibility to infection, mental disturbances, and diabetes mellitus.

ALLERGIC EMERGENCIES

Anaphylactic shock and conditions such as angioedema are medical emergencies that can result in cardiovascular collapse and death. They require prompt treatment of laryngeal edema, bronchospasm, and hypotension. Atopic individuals are particularly susceptible.

Insect stings and certain foods, including eggs, fish, cow's milk protein, peanuts, and tree nuts, are a risk for sensitized persons. Therapeutic substances particularly associated with anaphylaxis include blood products, vaccines, hyposensitizing (allergen) preparations, antibacterial (especially penicillins), iron injections, heparin, and neuromuscular-blocking drugs. Acetylsalicylic acid and other non-steroidal anti-inflammatory medicines (NSAIDs)

may cause bronchoconstriction in leukotriene-sensitive patients. In the case of drug allergy, anaphylaxis is more likely to occur after parenteral administration. Resuscitation facilities should always be available when injecting a drug associated with a risk of anaphylactic reactions. Anaphylactic reactions may also be associated with additives and excipients in foods and medicines. It is wise to check the full formula of preparations that may contain allergenic fats or oils.

First-line treatment of a severe allergic reaction includes administering **epinephrine (adrenaline)**, keeping the airway open (with assisted respiration if necessary), and restoring blood pressure (by laying the patient flat and raising the feet). Epinephrine (adrenaline) should be given immediately by intramuscular injection to produce vasoconstriction and bronchodilation; injection should be repeated, if necessary, at 5-minute intervals until blood pressure, pulse, and respiratory function have stabilized. If there is cardiovascular shock with inadequate circulation, epinephrine (adrenaline) must be given cautiously by slow intravenous injection of a dilute solution. Oxygen administration is also of primary importance.

An antihistamine (such as chlorphenamine by slow intravenous injection) is a useful adjunctive treatment, which should be given after epinephrine (adrenaline) injection and continued for 24–48 hours to reduce the severity and duration of symptoms and to prevent relapse. The onset of action of an intravenous corticosteroid (such as hydrocortisone) is delayed by several hours but it should also be given to help prevent later deterioration, especially in severely affected patients. Further treatment of anaphylaxis may include intravenous fluids, an intravenous vasopressor such as intravenous aminophylline, or an injected or nebulized bronchodilator such as salbutamol.

LML strengths and dosage forms are marked in *italic* with an asterisk.

Steps in the management of anaphylaxis

Sympathomimetic

Epinephrine (adrenaline), *by intramuscular injection* using epinephrine injection 1:1,000, **ADULT** and **ADOLESCENT**, 500 micrograms (0.5 ml); **INFANT** under 6 months, 50 micrograms (0.05 ml); **CHILD** 6 months–6 years, 120 micrograms (0.12 ml), 6–2 years, 250 micrograms (0.25 ml).

Note: The above doses may be repeated several times if necessary at 5-minute intervals, according to blood pressure, pulse, and respiratory function.

If circulation is inadequate, epinephrine (adrenaline) *by slow intravenous injection* using epinephrine injection 1:10,000 (given at a rate of 1 ml/min), **ADULT**, 500 micrograms (5 ml); **CHILD**, 10 micrograms/kg (0.1 ml/kg), given over several minutes.

Vital functions

Maintain an open airway; give oxygen by mask, restore blood pressure (lay patient flat, raise feet).

Antihistamine such as chlorphenamine, *by intravenous injection* over 1 minute, **ADULT**, 10–20 mg, repeated if required (max. total dose, 40 mg in 24 hours); **CHILD** 1 month–1 year, 250 micrograms/kg (maximum 2.5 mg); **CHILD** 1–5 years, 2.5–5 mg; **CHILD**, 6–12 years, 5–10 mg repeated if necessary up to 4 times daily.

Corticosteroids such as hydrocortisone *by slow intravenous injection*, **ADULT**, 100–300 mg; **CHILD** up to 1 year, 25 mg; **CHILD** 1–5 years, 50 mg; **CHILD** 6–12 years, 100 mg.

Intravenous fluids: Start *infusion* with sodium chloride, **ADULT** and **CHILD**, (0.5–1 L during the first hour).

If the patient has asthma-like symptoms, give salbutamol, 2.5–5 mg *by nebulization*, or aminophylline, 5 mg/kg *by intravenous injection*, over at least 20 minutes.

- **Chlorphenamine**

Chlorphenamine is a representative sedative antihistamine. Various medicines can serve as alternatives.

- **Dosage form**

- Injection: 10 mg/ml (hydrogen maleate) in 1 ml ampoule
- Tablet: 4 mg (hydrogen maleate)

- **Uses**

- Symptomatic relief of allergy, allergic rhinitis (hay fever) and conjunctivitis, urticaria, insect stings, and pruritus of allergic origin
- Adjunct in the emergency treatment of anaphylactic shock and severe angioedema

- **Precautions**

- Prostate enlargement, urinary retention
- Ileus or pyloroduodenal obstruction
- Glaucoma
- Child under 1 year
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Renal impairment: Appendix D
- Hepatic impairment: Appendix E
- Epilepsy

- **Interactions:** Appendix A
- **Skilled tasks:** Warn patient not to perform skilled tasks (such as operating machinery or driving) for 24 hours.

○ **Dose**

Allergy, by mouth

- **ADULT:** 4 mg every 4–6 hours (max, 24 mg daily)
- **CHILD** under 1 year: Not recommended
- **CHILD** 1–2 years: 1 mg twice daily
- **CHILD** 2–5 years: 1 mg every 4–6 hours (max. 6 mg daily)
- **CHILD** 6–12 years: 2 mg every 4–6 hours (max. 12 mg daily)

Allergic reactions, anaphylaxis (adjunct), by subcutaneous, intramuscular, or intravenous injection

- **ADULT:** 10–20 mg (max. 40 mg in 24 hours)
- **CHILD** 1 month–1 year: 250 micrograms/kg (max. 2.5 mg)
- **CHILD** 1–5 years: 2.5–5 mg
- **CHILD** 6–12 years: 5–10 mg

Dilution and administration: Give intravenous injection over 1 minute; if necessary, injection solution can be diluted with sodium chloride, 0.9% injection.

○ **Adverse effects**

- Drowsiness (rarely paradoxical stimulation with high doses, or in children or the elderly), hypotension, headache, dizziness, palpitations, psychomotor

impairment, urinary retention, dry mouth, blurred vision, gastrointestinal disturbances

- Liver dysfunction
- Blood disorders
- Also rash and photosensitivity reactions, sweating, and tremor
- Hypersensitivity reactions including bronchospasm, angioedema, and anaphylaxis
- Injections may be irritant

- **Diphenhydramine**

- **Dosage form**

- Tablet: 25 mg and 50 mg (as hydrochloride)
 - Oral syrup: 5 mg/5 ml (as hydrochloride)

- **Uses**

- Symptomatic treatment of allergy, including pruritis, urticaria, and angioedema
 - Rhinitis and conjunctivitis
 - Nausea and vomiting especially in prevention and treatment of motion sickness
 - Vertigo, control of Parkinson's symptoms, extrapyramidal symptoms related to drug (however, diphenhydramine itself may cause extrapyramidal effects)
 - Short-term treatment of insomnia, cough, and cold

- **Contraindications**

- Child under 2 years

- **Precautions**

- Porphyria
- Pregnancy and breast-feeding
- **Interactions:** Appendix A

- **Dose**

- **ADULT:** In the above mentioned conditions, *by mouth*, 25–50 mg 3–4 times daily
- **CHILD** 6.25–25 mg 3–4 times daily or 5 mg/kg daily in divided doses
- Maximum daily dose for **ADULT** and **CHILD** is 300 mg

Hypnosis

- **ADULT** and **CHILD** over 12 years: 20–50 mg daily

- **Adverse effects**

- Psychosis, convulsions, mydriasis, tachycardia
- Respiration irregularities reported

- **Epinephrine (adrenaline)**

- **Dosage form**

- Injection 0.1% (as hydrochloride or hydrogen tartrate) in 1 ml ampoule

Note: Different dilutions of epinephrine injection are used for different routes of administration.

- **Uses**

- Severe anaphylactic reaction
- Severe angioedema
- Cardiac arrest (Section 12.2)

- **Precautions**

- Hyperthyroidism, hypertension, diabetes mellitus, heart disease, arrhythmias, cerebrovascular disease
- Second stage of labor
- Elderly

- **Interactions**

- Severe anaphylaxis in patients on non-cardioselective beta-blockers (for example, propranolol), may not respond to epinephrine (adrenaline) injection, calling for intravenous injection of salbutamol (Section 25.1).
- 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 adrenaline. *See also* Appendix A

- **Dose**

- Anaphylaxis, *by intramuscular or subcutaneous injection* of 1:1,000 epinephrine injection; *see* Steps in the management of anaphylaxis (box above) for doses

- Anaphylaxis, *by slow intravenous injection* of 1:10,000 epinephrine injection.

This route should be reserved for severely ill patients when there is doubt about the adequacy of circulation and absorption from the intramuscular site; see Steps in the management of anaphylaxis (box above) for doses.

- **Adverse effects**

- Tachycardia and arrhythmias, hypertension, tremor, anxiety, sweating, nausea, vomiting, weakness, hyperglycemia, dizziness, and pulmonary edema have all been reported
- Headache common

- **Hydrocortisone**

- **Dosage form**

- Injection: 100 mg (as sodium succinate) and 25 mg/mL* (as sodium acetate) in vial

- **Uses**

- Adjunct in the emergency treatment of anaphylaxis
- Inflammatory skin conditions (Section 13.3)
- Inflammatory bowel disease (Section 17.3)
- Treatment of malignant neoplasia (Section 8.2)
- Adrenocortical insufficiency (Section 18.1)

- **Contraindications**

- Not relevant to emergency use but for contraindications relating to long-term use, see Section 18.1

- **Precautions**

- Not relevant to emergency use but for precautions relating to low-dose, long-term use, *see* Section 18.1

- **Dose**

- Anaphylaxis (adjunct), *by slow intravenous injection* as a single dose; *see* Steps in the management of anaphylaxis (box above).

- **Adverse effects**

- For adverse effects associated with long-term corticosteroid treatment, *see* Section 18.1.

- **Prednisolone**

Prednisolone is a representative corticosteroid. Various medicines can serve as alternatives.

- **Dosage form**

- Tablet: 5 mg

- **Uses**

- Short-term suppression of inflammation in allergic disorders
- Longer-term suppression (Section 18.1)
- Malignant disease (Section 8.3)
- Inflammation of the eye (Section 21.2)

- **Contraindications**

- Untreated systemic infection
- Administration of live virus vaccines

- **Precautions**

- Increased susceptibility to, and severity of, infection

- Activation or exacerbation of tuberculosis, amebiasis, and strongyloidiasis
- Risk of severe chicken pox in non-immune patients (varicella-zoster immunoglobulin required if exposed to chicken pox)
- Avoid exposure to measles (normal immunoglobulin possibly required if exposed)
- Diabetes mellitus
- Peptic ulcer
- Hypertension
- Corneal perforation
- For further precautions, in particular, those relating to low-dose, long-term use of corticosteroids, *see* Section 18.1.

- **Dose**

Allergy (short-term use), by mouth

- **ADULT** and **CHILD**: Initially up to 10–20 mg daily as a single dose in the morning (in severe allergy, up to 60 mg daily as a short course of 5–10 days)

- **Adverse effects**

- Nausea, dyspepsia, malaise, hiccups
- Hypersensitivity reactions including anaphylaxis
- For adverse effects associated with long-term corticosteroid treatment, *see* Section 18.1.

- **Promethazine**

- **Dosage form**

- Injection: 25 mg/ml in 2 ml ampoule

- Tablet: 25 mg
- Oral syrup: 5 mg/5 ml (as hydrochloride)

- **Uses**

- Symptomatic relief of allergy such as hay fever and urticaria
- Emergency treatment of anaphylactic reactions
- Sedation (Section 1.3)
- Nausea and vomiting (Section 17.2)

- **Contraindications**

- See Section 17.2

- **Precautions**

- See Section 17.2.

- **Dose**

By mouth

- **ADULT:** 10–20 mg 2–3 times daily
- **CHILD** 2–5 years: 5–15 mg daily in 1–2 divided doses
- **CHILD** 5–10 years: 10–25 mg daily in 1–2 divided doses

By deep intramuscular injection

- **ADULT:** 25–50 mg (max. 100 mg)
- **CHILD** 5–10 years: 6.25–12.5 mg

By slow intravenous injection in emergencies

- **ADULT:** 25–50 mg as a solution containing 2.5 mg/ml in water for injections
(max. 100 mg)

- **Adverse effects**

- Drowsiness is a significant side effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.
- Side effects that are more common with the older antihistamines include headache, psychomotor impairment, and antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastrointestinal disturbances.
- Other rare side effects of antihistamines include hypotension, palpitation, arrhythmias, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, hypersensitivity reactions (including bronchospasm, angioedema, and anaphylaxis, rashes, and photosensitivity reactions), blood disorders, liver dysfunction, and angle-closure glaucoma.
- Also restlessness
- Intramuscular injection may be painful.

SECTION 4: Antidotes and other substances used in poisonings

These notes are only guidelines and it is strongly recommended that poison information centers be consulted in cases where there is doubt about the degree of risk or about appropriate management.

LML strengths and dosage forms are marked in *italic* with an asterisk.

4.1 NON-SPECIFIC

Ideally, all patients who show features of poisoning should be admitted to the hospital.

Patients who have taken poisons with delayed action should also be admitted, even if they appear well; delayed-action poisons include acetylsalicylic acid, iron, lithium, paracetamol, paraquat, tricyclic antidepressants, and warfarin. The effects of modified-release or prolonged-release preparations are also delayed. It is often impossible to establish with certainty the identity of the poison and the size of the dose but information on the type and timing of poisoning may be useful for symptomatic management. Few patients require active removal of the poison.

Most patients must be treated symptomatically and monitored. 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 that are prolonged or recurrent may be controlled by intravenous diazepam.

In rare situations, removal of the poison from the stomach by gastric lavage may be appropriate (*see below*). More commonly, activated charcoal, which can bind many poisons in the stomach and therefore prevent absorption, is the preferred course of treatment for poisoning. Active elimination techniques such as repeated administration of activated charcoal can enhance the elimination of some drugs after they have been absorbed (*see below*). Other techniques to enhance elimination of poisons after their absorption are practical only in the hospital and are suitable for only a small number of patients and a

limited number of poisons. Methods include hemodialysis and hemoperfusion. Alkalinization of urine can be used to increase the elimination of salicylates. Forced alkaline diuresis is no longer recommended.

Gastric lavage

Gastric lavage is rarely required and should be considered only if a life-threatening amount of a substance that cannot be removed effectively by other means (for example, iron), has been ingested within the last hour. Gastric emptying is clearly unnecessary if the risk of toxicity is small or if the patient presents too late. The main risk is inhalation of stomach contents; thus gastric lavage should **NOT** be undertaken unless the airway can be protected adequately.

Gastric lavage must **NOT** be attempted after corrosive poisoning or for hydrocarbon products, which could be dangerous if aspirated.

Emesis

Induction of emesis for the treatment of poisoning is **NOT RECOMMENDED**. There is no evidence that it affects absorption of the poison, and it may increase the risk of aspiration.

Furthermore, the effects of the emetic substance may complicate diagnosis.

Prevention of absorption

Given by mouth, **activated charcoal** can bind many poisons in the gastrointestinal system, thereby reducing their absorption. Generally speaking, the sooner it is given, the more effective it is, and it is most effective if administered within 1 hour of ingestion of the poison. It may be effective several hours after poisoning with modified-release preparations or drugs with anticholinergic (antimuscarinic) properties. It is relatively safe and particularly useful for prevention of absorption of poisons that are toxic in small amounts—for example,

antidepressants. Furthermore, repeated doses of activated charcoal enhance the fecal elimination of some drugs (which undergo enterohepatic or enteroenteric recycling) several hours after ingestion and after they have been absorbed—for example, phenobarbital and theophylline.

- **Charcoal, activated**

- **Dosage form**

- Tablets: 500 mg and 1g
 - Powder

- **Uses**

- Treatment of acute poisoning

- **Contraindications**

- Poisoning by hydrocarbons with high potential for harm if aspirated
 - Poisoning by corrosive substances (may prevent visualization of lesions caused by the poison)

- **Precautions**

- Drowsy or unconscious patients (risk of aspiration; intubate before administration via nasogastric or gastric tube)
 - Not effective for poisoning with alcohols, clofenotane (dicophane, [DDT]), cyanides, malathion, and metal salts including those of iron and lithium

- **Dose**

Poisoning (reduction of absorption), by mouth, as soon as possible after ingestion of poison

- **ADULT:** 50–100 g as a single dose
- **INFANT:** 1 g/kg as a single dose
- **CHILD** 1–12 years: 25 g as a single dose (50 g in severe poisoning)

Poisoning (active elimination), by mouth

- **ADULT:** 50 g every 4 hours (in case of intolerance, 25 g every 2 hours)
- **INFANT:** 1 g/kg every 4–6 hours
- **CHILD** over 1 year: 25–50 g every 4–6 hours

- **Adverse effects**

- Black stools
- Vomiting, constipation, or diarrhea
- Pneumonitis (due to aspiration)

4.2 SPECIFIC

Paracetamol overdose

As little as 10–15 g or 150 mg/kg of paracetamol taken within 24 hours may cause severe hepatocellular necrosis and much less frequently, renal tubular necrosis. The only early features of poisoning, nausea and vomiting, usually settle within 24 hours. Persistence beyond this time, often with the onset of right sub-costal pain and tenderness, usually indicates the development of liver damage, which is maximal 3–4 days after ingestion. Despite a lack of significant early symptoms, patients who have taken an overdose of paracetamol should be transferred to the hospital urgently.

Administration of activated charcoal should be considered if paracetamol in excess of 150 mg/kg or 12 g, whichever is smaller, is thought to have been ingested within the previous hour.

Acetylcysteine protects the liver if given within 24 hours of ingesting paracetamol.

Acetylcysteine, given intravenously, is most effective if administered within 8 hours of overdose, after which its effectiveness declines sharply. Alternatively, in remote areas, if acetylcysteine cannot be given promptly, **DL-methionine** may be given by mouth provided the overdose was ingested within 10–12 hours and the patient is not vomiting. However, acetylcysteine is the preferred treatment. Concurrent use of activated charcoal and specific oral antidotes should be avoided. Once the patient is in the hospital, the need to continue antidote treatment can be assessed from plasma paracetamol concentration.

Opioid analgesic overdose

Opioids cause coma, respiratory depression, and pinpoint pupils. **Naloxone** is a specific antidote indicated if there is coma or bradypnea. Naloxone has a shorter duration of action than many opioids, so close monitoring and repeated injections are required according to respiratory rate and depth of coma; alternatively, naloxone may be given by continuous intravenous infusion and the rate of infusion adjusted according to vital signs. The effects of some opioids, such as buprenorphine, are only partially reversed by naloxone.

Acute withdrawal syndromes may be precipitated by the use of naloxone in patients with a physical dependence on opioids or in overdose with large doses; a withdrawal syndrome may occur in neonates of opioid-dependent mothers.

Organophosphate and carbamate poisoning

Organophosphates are absorbed through the bronchi and intact skin as well as from the gastrointestinal tract. Initial treatment of organophosphate or carbamate poisoning includes prevention of further absorption by moving the patient to fresh air, removing contaminated clothing, and washing contaminated skin. A clear airway must be maintained. Gastric lavage may be considered if the airway is protected.

Organophosphates inhibit cholinesterases and thus prolong the effects of acetylcholine. Toxicity depends on the particular compound involved, and onset after skin exposure may be delayed. **Atropine** will reverse the muscarinic effects of acetylcholine and is used (in conjunction with oximes, such as pralidoxime, and additional symptomatic treatment.

Additional treatment for carbamate poisoning is generally symptomatic and supportive. Atropine may be given but may not be required because of the rapidly reversible type of cholinesterase inhibition produced.

Iron poisoning and iron and aluminium overload

Mortality from iron poisoning is reduced by specific therapy with **deferoxamine**, which chelates iron. Before administration of deferoxamine, the stomach should be emptied by gastric lavage (with a wide-bore tube), preferably within 1 hour of ingesting a significant quantity of iron or if radiography reveals tablets in the stomach. Deferoxamine is also used to diagnose and treat chronic iron overload. It is used in the diagnosis of aluminium overload and to treat aluminium overload in patients with end-stage renal failure undergoing maintenance hemodialysis.

Heavy metal poisoning

Heavy metal poisoning may be treated with a range of antidotes, including **dimercaprol**, **penicillamine**, **potassium ferric hexacyanoferrate**, and **sodium calcium edetate**.

Penicillamine is also used to promote excretion of copper in Wilson's disease.

Methemoglobinemia

Methylthioninium chloride can lower the levels of methemoglobin in red blood cells and is used in the treatment of methemoglobinemia. In large doses, it may cause methemoglobinemia; therefore, methemoglobin levels should be monitored during treatment.

Cyanide poisoning

Cyanide poisoning may be treated with **sodium nitrite** followed by **sodium thiosulfate**.

- **Acetylcysteine**
 - **Dosage form**
 - Injection: 200 mg/ml in 10 ml ampoule
 - Tablet: 200 mg
 - Syrup: 200 mg/5 ml
 - **Uses**
 - Paracetamol overdose
 - **Precautions**
 - Asthma (see Adverse effects below, but do not delay treatment)
 - **Dose**

Paracetamol overdose, by intravenous infusion

- **ADULT** and **CHILD**: Initially 150 g/kg over 15 minutes, then 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours.

Administration: Dilute requisite dose in glucose intravenous infusion solution, 5% as follows:

- **ADULT** and **CHILD** over 12 years: Initially 200 ml given over 15 minutes, then 500 ml over 4 hours, then 1 L over 16 hours
- **CHILD** under 12 years with a body weight over 20 kg: Initially 100 ml given over 15 minutes, then 250 ml over 4 hours, then 500 ml over 16 hours
- **CHILD** under 12 years with a body weight under 20 kg: Initially 3 ml/kg given over 15 minutes, then 7 ml/kg over 4 hours, then 14 ml/kg over 16 hours

Note: Manufacturer may recommend other infusion fluids, but glucose solution, 5%, is preferable.

○ **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, chlorphenamine) and acute asthma with a short-acting beta2- agonist, such as salbutamol (see Section 25.1)

- **Atropine sulfate**

- **Dosage form**

- Injection: 0.5 mg/ml and 1 mg/ml in 1ml ampoule

- **Uses**

- Organophosphate and carbamate poisoning
 - Preoperative and intraoperative medication (Section 1.3)
 - Mydriasis and cycloplegia (Section 21.5)

- **Precautions**

- Children
 - Elderly
 - Down syndrome
 - Angle-closure glaucoma
 - Myasthenia gravis
 - Gastrointestinal disorders
 - Prostatic enlargement
 - Cardiac disorders
 - Hypoxia
 - Pyrexia and in warm environments (monitor temperature and keep patients cool)
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A

- **Dose**

*Organophosphate poisoning, by intramuscular or intravenous injection
(depending on severity of poisoning)*

- **ADULT:** 2 mg (**CHILD:** 20 micrograms/kg) every 5–10 minutes until the skin becomes flushed and dry, the pupils dilate, and tachycardia develops

- **Calcium gluconate**

- **Dosage form**

- Injection: 10% in 10 ml ampoule

- **Uses**

- Hypocalcemic tetany: *See* Section 27.

- **Deferoxamine**

- **Dosage form**

- Powder for injection: 500 mg (mesylate) in vial

- **Uses**

- Acute iron poisoning
- Chronic iron overload
- Aluminium overload

- **Precautions**

- Renal impairment: Appendix D

- Eye and ear examinations are advised before and at 3-month intervals during treatment
- Aluminium encephalopathy (may exacerbate neurological dysfunction)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Children under 3 years (may retard growth)

○ **Dose**

Acute iron poisoning, by slow intravenous infusion

- **ADULT and CHILD:** 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 subcutaneous or intravenous infusion

- **ADULT and CHILD:** Lowest effective dose (usually within range of 20–60 mg/kg/day) 4–7 days per week

Aluminium overload in end-stage renal failure, by intravenous infusion

- **ADULT and CHILD:** 5 mg/kg, once a week during last hour of dialysis

Diagnosis of iron overload, by intramuscular injection

- **ADULT and CHILD:** 500 mg

Diagnosis of aluminium overload, by intravenous infusion

- **ADULT and CHILD:** 5 mg/kg during last hour of dialysis

Reconstitution and administration: According to manufacturer's directions. For full details and warnings relating to administration for therapeutic or diagnostic purposes, consult manufacturer's literature.

- **Adverse effects**

- Hypotension (especially when given too rapidly by intravenous injection), disturbances of hearing and vision (including lens opacity and retinopathy)
- Injection-site reactions, gastrointestinal disturbances, asthma, fever, headache, arthralgia, and myalgia
- Very rarely anaphylaxis, acute respiratory distress syndrome, neurological disturbances (including dizziness, neuropathy, and paresthesia), Yersinia and mucormycosis infections, rash, renal impairment, and blood dyscrasias

- **Dimercaprol**

- **Dosage form**

- Injection in oil: 50 mg/ml in 2 ml and 100 mg/ml in 3 ml ampoules

- **Uses**

- Acute poisoning by antimony, arsenic, bismuth, gold, mercury, possibly thallium
- Adjunct (with sodium calcium edetate) in lead poisoning

- **Contraindications**

- Iron, selenium, and cadmium poisoning
- Severe hepatic impairment (unless due to arsenic poisoning)

- **Precautions**

- Hypertension
- Renal impairment (discontinue or use with extreme caution if impairment develops during treatment; *see also* Appendix D)
- Any abnormal reaction such as hyperpyrexia should be assessed
- Elderly

- Pregnancy and breast-feeding: Appendix C
- **Interactions:** Appendix A
- **Dose**

Poisoning by heavy metals, by intramuscular injection

 - **ADULT and CHILD:** 2.5–3 mg/kg every 4 hours for 2 days, 3 mg/kg 2–4 times on the third day, then 3 mg/kg 1–2 times daily for 10 days or until recovery
- **Adverse effects**
 - Hypertension, tachycardia
 - Malaise, nausea, vomiting, abdominal pain, salivation, lacrimation, sweating, burning sensation in the mouth, throat, and eyes
 - Feeling of constriction in the throat and chest
 - Headache, muscle spasms, tingling of the extremities
 - Fever in children
 - Local pain and abscess at injection site
- **Flumazenil**
 - **Dosage form**
 - Injection: 0.1 mg/ml and 0.5 mg/ml
 - **Uses**
 - Reversal of sedative effects of benzodiazepines in anesthetic, intensive care, and diagnostic procedures
 - Overdosage of benzodiazepines (see below)

- **Contraindications**

- Life-threatening condition (e.g., raised intracranial pressure, status epilepticus) controlled by benzodiazepines

Overdosage of benzodiazepines: Benzodiazepines taken alone cause drowsiness, ataxia, dysarthria, nystagmus, and occasionally respiratory depression, and coma.

Activated charcoal can be given within 1 hour of ingesting a significant quantity of benzodiazepine, provided the patient is awake and the airway is protected.

Benzodiazepines potentiate the effects of other central nervous system depressants taken concomitantly. Use of the benzodiazepine antagonist flumazenil (unlicensed indication) can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients. Flumazenil may prevent the need for ventilation, particularly in patients with severe respiratory disorders; it should be used on expert advice only and not as a diagnostic test in patients with a reduced level of consciousness.

- **Precautions**

- Short-acting (repeat doses may be necessary—benzodiazepine effects may persist for at least 24 hours)
- Benzodiazepine dependence (may precipitate withdrawal symptoms)
- Prolonged benzodiazepine therapy for epilepsy (risk of convulsions)
- History of panic disorders (risk of recurrence)
- Ensure neuromuscular blockade cleared before giving
- Avoid rapid injection in high-risk or anxious patients and following major surgery

- Head injury (rapid reversal of benzodiazepine sedation may cause convulsions)
- Elderly
- Children
- Hepatic impairment: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Dose**
 - By intravenous injection*
 - **ADULT:** 200 micrograms over 15 seconds, then 100 micrograms at 60-second intervals if required; usual dose range, 300–600 micrograms; maximum total dose 1 mg (2 mg in intensive care); question etiology if no response to repeated doses
 - By intravenous infusion, if drowsiness recurs after injection*
 - **ADULT:** 100–400 micrograms/hour, adjusted according to level of arousal
 - By intravenous injection*
 - **CHILD** 1 month–12 years: 10 micrograms/kg (max. single dose 200 micrograms), repeated at 1-minute intervals if required; maximum total dose of 40 micrograms/kg (1 mg) (2 mg in intensive care)
 - **CHILD** 12–18 years: 200 micrograms, repeated at 1-minute intervals if required; maximum total dose 1 mg (2 mg in intensive care)
 - By intravenous infusion, if drowsiness recurs after injection*
 - **NEONATE:** 2–10 micrograms/kg/hour, adjusted according to response
 - **CHILD** 1 month–18 years: 2–10 micrograms/kg/hour, adjusted according to response; maximum 400 micrograms/hour

- **Adverse effects**
 - Nausea, vomiting, and flushing
 - If wakening too rapid, agitation, anxiety, and fear
 - Transient increase in blood pressure and heart rate in intensive care patients
 - Very rarely convulsions (particularly in those with epilepsy), confusion, sensation disorders, chills, and sweating
 - Hypersensitivity reactions, including anaphylaxis
- **Methylthioninium chloride (methylene blue)**
 - **Dosage form**
 - Injection: 10 mg/ml in 10 ml ampoule
 - **Uses**
 - Acute methemoglobinemia
 - **Contraindications**
 - Severe renal impairment
 - Methemoglobinemia due to chlorate or induced by sodium nitrite in treatment of cyanide poisoning
 - **Precautions**
 - G6PD deficiency (may cause hemolytic anemia)
 - Monitor blood methemoglobin throughout treatment
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Dose**

Acute methemoglobinemia, by slow intravenous injection over several minutes

- **ADULT and CHILD:** 1–2 mg/kg as a single dose; may be repeated after 1 hour if required

Administration: According to manufacturer's directions

- **Adverse effects**

- Nausea, vomiting, abdominal pain, chest pain, headache, dizziness, confusion, profuse sweating
- Hypertension or hypotension reported
- Hemolytic anemia (in G6PD deficiency)
- Methemoglobinemia (with high dosage)
- Bluish skin discoloration
- Blue saliva, urine, and feces

- **Naloxone**

- **Dosage form**

- Injection: 400 micrograms/ml (hydrochloride) in 1 ml ampoule

- **Uses**

- Opioid overdose
- Postoperative respiratory depression

- **Precautions**

- Physical dependence on opioids or other situations where acute withdrawal syndrome may be precipitated (*see above under Opioid analgesic overdose*)
- Cardiovascular disease
- Pregnancy: Appendix B

- **Dose**

Overdosage of opioids, by intravenous injection

- **ADULT:** 0.4–2 mg repeated at intervals of 2–3 minutes up to a maximum of 10 mg; question diagnosis if respiratory function does not improve
- **CHILD:** 10 micrograms/kg; a subsequent dose of 100 micrograms/kg may be given if no response

Note: Naloxone hydrochloride may be administered in the same doses by intramuscular or subcutaneous injection, but only if the intravenous route is not feasible (slower onset of action).

Overdosage of opioids, by continuous intravenous infusion using an infusion pump

- **ADULT:** 10 mg diluted in 50 ml glucose intravenous infusion solution, 5% at a rate adjusted according to response (initial infusion rate may be set to deliver 60% of intravenous dose [see above] over 1 hour)

- **Adverse effects**

- Nausea, vomiting, and sweating (may also be due to opioid withdrawal)

- **Penicillamine**

- **Dosage form**

- Capsules or tablets: 125 mg and 250 mg

- **Uses**

- Poisoning by heavy metals, particularly lead and copper
- Wilson's disease

- Severe rheumatoid arthritis (Section 2.4)
- **Contraindications**
 - Hypersensitivity
 - Lupus erythematosus
- **Precautions**
 - Monitor throughout treatment (including blood counts and urine tests).
 - Renal impairment: Appendix D
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Avoid concurrent gold, chloroquine, or immunosuppressive treatment.
 - Avoid oral iron within 2 hours of a dose.
 - Penicillin hypersensitivity (risk of cross-reactivity)
 - **Interactions:** Appendix A
 - **Blood counts:** In Wilson's disease, consider withdrawal if platelet count falls below $120,000/\text{mm}^3$ or white blood cells fall below $2,500/\text{mm}^3$ or if 3 successive falls are recorded (can restart at reduced dose when counts return to within a reference range but permanent withdrawal is necessary if neutropenia or thrombocytopenia recur)

Patient advice: In Wilson's disease, warn patient to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, or rash develop.

- **Dose**

Lead poisoning, by mouth

- **ADULT:** 1–2 g daily in divided doses before food (continue until urinary lead stabilized at less than 500 micrograms/day)
- **CHILD:** 20 mg/kg daily in divided doses

Wilson's disease, by mouth

- **ADULT:** 1.5–2 g daily in divided doses before food (max. 2 g daily for 1 year), thereafter 0.75–1 g daily
- **ELDERLY:** 20 mg/kg daily in divided doses adjusted according to response
- **CHILD:** Up to 20 mg/kg daily in divided doses (min. 500 mg daily)
- **Adverse effects**
 - See Section 2.4.

- **Pralidoxime**

- **Dosage form**
 - Injection: 500 mg/ml (as chloride)
- **Uses**
 - Adjunct to atropine in the treatment of poisoning by organophosphorus insecticide or nerve agent
- **Contraindications**
 - Poisoning with carbamates or with organophosphorus compounds without anticholinesterase activity
- **Precautions**
 - Myasthenia gravis
 - Renal impairment: Appendix D

- **Dose**

By intravenous infusion

- **ADULT** and **CHILD**: Initially 30 mg/kg over 20 minutes, followed by 8 mg/kg/hour; usual maximum 12 g in 24 hours

Note: The loading dose may be administered *by intravenous injection* (diluted to a concentration of 50 mg/ml with water for injections) over at least 5 minutes if pulmonary edema is present or if it is not practical to administer an intravenous infusion.

- **Adverse effects**

- Drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation, and muscular weakness

- **Protamine sulfate**

- **Dosage form**

- Injection: 10 mg/ml in 5 ml ampoule

- **Uses**

- Antidote to over dosage with heparin sodium

- **Precautions**

- If used in excess, protamine sulfate has an anticoagulant effect.
- Previous treatment with protamine or protamine insulin, fish allergies, and men who are infertile or who have had a vasectomy (increased risk of allergic reactions)

- **Dose**

Heparin overdose, by intravenous injection over approximately 10 minutes

- **ADULT:** 1 mg neutralizes 80–100 IU heparin sodium when given within 15 minutes; if longer time, less protamine is needed as heparin is rapidly excreted

- **Adverse effects**

- Nausea, vomiting, lassitude, flushing, hypotension, bradycardia, dyspnea, allergic reactions, including angioedema and anaphylaxis

SECTION 5: Anticonvulsants/anti-epileptics

CONTROL OF EPILEPSY

Treatment should always commence with a single drug, the choice of which can only be made on an individual basis and will depend on the efficacy of the drug and the patient's tolerance of treatment. If a drug fails to control the seizures after it has been used in full therapeutic dosage for an adequate period, or if it is not tolerated, it should be gradually substituted with another, with the first drug being withdrawn only when the new regimen is fully established. If monotherapy is ineffective, two drugs should be given in combination. Several regimens may need to be tried before the most appropriate is found.

The initial dose of the chosen drug should be determined on the basis of the degree of urgency and the size and the age of the patient. It should be increased gradually until an effective response is obtained. All anti-epileptics commonly produce neurological adverse effects at too high a dose, and patients should be monitored closely for adverse effects to help in accurate dose titration. However, except for phenytoin, it is rarely useful to measure plasma drug concentrations as an aid to dose adjustment. Non-compliance because of inappropriate dosing and overdosing is a major impediment to effective anti-epileptic treatment. Patients should ideally remain under supervision throughout treatment.

Withdrawal

Treatment is normally continued for a minimum of 2 years after the last seizure. Withdrawal should be extended over a period of several months because abrupt withdrawal can lead to complications such as status epilepticus. In patients receiving several anti-epileptic drugs, only one drug should be withdrawn at a time. Many adult patients relapse once treatment is

withdrawn and it may be necessary to continue treatment indefinitely, particularly when the patient's livelihood or lifestyle can be endangered by recurrence of a seizure.

Pregnancy and breast-feeding

Untreated epilepsy during pregnancy may cause harm to the fetus; there is therefore no justification for abrupt withdrawal of treatment in women who become pregnant, although withdrawal of therapy may be an option if the patient has been seizure-free for at least 2 years; resumption of treatment may be considered after the first trimester. If anti-epileptics are continued in pregnancy, monotherapy with the lowest effective dose is preferred, with adjustment made to take account of changes in plasma drug concentration associated with pregnancy. There is an increased risk of birth defects with the use of an anti-epileptic, particularly with carbamazepine, valproic acid, and phenytoin. However, if there is good seizure control, there is probably no advantage in changing pregnant patients' anti-epileptic drugs. In view of the risks of neural tube and other defects, patients who may become pregnant should be informed of the risks and referred for advice, and pregnant patients should be offered counseling and antenatal screening. To counteract the risk of neural tube defects, adequate folate supplements are advised for women before and during pregnancy. In view of the risk of neonatal bleeding associated with carbamazepine, phenobarbital, and phenytoin, prophylactic phytonadione (vitamin K1) is recommended for the neonate and the mother before delivery. Anti-epileptic drugs can be continued during breast-feeding.

Driving

In many countries, regulations are in place that may, for example, restrict driving by patients with epilepsy to those whose seizures are controlled. Furthermore, anti-epileptic and anticonvulsant drugs may cause central nervous system depression, particularly in the early

stages of treatment, and patients who experience adverse effects such as drowsiness or dizziness should not operate machinery or drive.

CHOICE OF ANTI-EPILEPTIC IN THE MANAGEMENT OF CONVULSIVE DISORDERS

Generalized tonic-clonic, simple partial, and complex partial seizures

Carbamazepine, phenobarbital, phenytoin, and valproic acid are widely used in the treatment of these conditions. However, each of these drugs is associated with dose-related and idiosyncratic adverse effects and monitoring of hematological and hepatic function is often advised, particularly for carbamazepine and valproic acid.

Absence seizures

Both **ethosuximide** and **valproic acid** are widely used in the treatment of absence seizures (petit mal) and are usually well tolerated. However, ethosuximide can, rarely, cause lupus erythematosus and psychoses, which call for immediate, but cautious, discontinuation. Moreover, as absence seizures are commonly associated with tonic-clonic seizures, valproic acid is often preferred since it is effective in both disorders.

Tonic seizures, atonic seizures, and atypical absence seizures

Phenobarbital and **phenytoin** are widely used for tonic seizures, and **valproic acid** for atonic seizures and for atypical absence seizures.

Myoclonic seizures

Valproic acid is widely used and most effective for juvenile myoclonic seizures. However, both valproic acid and this type of seizure are associated with a high relapse rate, and it is often necessary to continue therapy indefinitely. Other myoclonic seizures are often resistant to treatment, and some do not have an epileptic basis. Valproic acid can be of value in this case, and other anti-epileptic drugs may be useful in intractable cases.

Infantile spasm (infantile myoclonic epilepsy)

Infantile spasms, which are often associated with severe brain damage, can be resistant to anti-epileptic drugs. **Vigabatrin** or **valproic acid** (alone or in combination with clonazepam) are used.

Febrile convulsions

Brief febrile convulsions usually respond to sponging with tepid water and the giving of an antipyretic such as paracetamol. Recurrent febrile convulsions or prolonged convulsions (those lasting 15 minutes or longer) are treated with **diazepam**, either rectally in solution or by intravenous injection, to prevent possible brain damage. *Intermittent prophylaxis* with diazepam administered at the onset of fever may prevent recurrence of febrile convulsions but only in a small proportion of children, and its routine use in this way is not recommended. Use of anti-epileptics for *continuous prophylaxis* is controversial; it is probably indicated in only a small proportion of children, including those whose first seizure occurred during the first 14 months of life, or who already have evident neurological abnormalities, or who have had previous prolonged or focal convulsions. **Phenobarbital** may be used for this purpose but careful clinical monitoring and dosage adjustment are necessary in order to minimize the

risk of adverse effects. **Valproic acid**, although effective, is not recommended because of the greater risk of hepatotoxicity in young children.

Status epilepticus

Status epilepticus is a medical emergency that carries a high mortality rate. Initial management includes positioning the patient to avoid injury, supporting respiration (including provision of oxygen), maintaining blood pressure, and the correction of any hypoglycemia; maintenance of the airway and assisted ventilation are crucial even when the seizures are controlled, because the drugs used in their management may also depress respiration. The use of parenteral thiamine should be considered if alcohol abuse is suspected; pyridoxine should be administered if the status epilepticus is likely to be responsive to pyridoxine.

Intravenous **diazepam** is often effective in status epilepticus. Diazepam, which acts rapidly, should be administered first and should be followed immediately by a loading dose of **phenytoin**, which has a longer-acting effect. When cannulation is impossible, diazepam may be administered rectally as a solution (absorption from suppositories is too slow for treatment of status epilepticus). Intravenous **phenobarbital** is also effective but is more likely to cause respiratory depression; it is used in refractory cases but should be avoided in patients who have recently received oral phenobarbital. Rectal paraldehyde may also be used; it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor. If seizures continue despite treatment, general anesthesia may be required. The underlying cause must be identified and remedied in all cases.

Eclampsia and pre-eclampsia

Magnesium sulfate has a major role in eclampsia for the prevention of recurrent seizures.

Monitoring of blood pressure, respiratory rate, and urinary output is necessary, as is monitoring for clinical signs of overdosage (loss of patellar reflexes, weakness, nausea, sensation of warmth, flushing, double vision, and slurred speech). Calcium gluconate injection (Section 27) is used for the management of magnesium toxicity. Magnesium sulfate is also used in women with pre-eclampsia who are at risk of developing eclampsia; careful monitoring of the patient (as described above) is necessary.

LML strengths and dosage forms are marked in *italic* with an asterisk.

- **Carbamazepine**

- **Dosage form**

- Tablets: 100 mg and 200 mg

- **Uses**

- Generalized tonic-clonic and partial seizures
 - Trigeminal neuralgia
 - Bipolar disorders (Section 24.2.2)

- **Contraindications**

- Atrioventricular conduction abnormalities
 - History of bone marrow depression
 - Porphyria

- **Precautions**

- Hepatic impairment: Appendix E
 - Renal impairment: Appendix D

- Cardiac disease (*see also* Contraindications)
- Skin reactions (*see* Adverse effects)
- History of blood disorders (monitor blood counts before and during treatment)
- Glaucoma
- Pregnancy (important—*see* above, Pregnancy and breast-feeding under Control of Epilepsy): Appendix B
- Breast-feeding (*see* above, Pregnancy and breast-feeding under Control of Epilepsy): Appendix C
- Avoid sudden withdrawal (*see* above, Withdrawal under Control of Epilepsy)
- **Interactions:** Appendix A
- **Blood, hepatic, or skin disorders:** Patients or their carers 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 that is severe, progressive, and associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative anti-epileptic).
- **Skilled tasks:** Warn patient not to perform skilled tasks (such as operating machinery or driving) for 24 hours. *See also* introductory notes to Section 5 above.

○ **Dose**

Generalized tonic-clonic seizures, partial seizures, by mouth

- **ADULT:** 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)

- **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

Trigeminal neuralgia, by mouth

- **ADULT:** 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 micromole/L)

○ **Adverse effects**

- Dizziness, drowsiness, headache, ataxia, blurred vision, diplopia (may be associated with high plasma levels)
- Gastrointestinal intolerance including nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhea 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 anemia)
- Cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia,

thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paresthesia, depression, impotence, male infertility, gynecomastia, galactorrhea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatremia, edema, and disturbances of bone metabolism with osteomalacia also reported

- Confusion and agitation in the elderly

- **Diazepam**

Diazepam is a representative benzodiazepine anticonvulsant. Various drugs can serve as alternatives.

- **Dosage form**

- Injection: 5 mg/ml in 2 ml ampoule (intravenous)
- Tablets: 2 mg, 5 mg, and 10 mg

- **Uses**

- Epilepsy, status epilepticus
- Emergency management of recurrent seizures
- Recurrent or prolonged febrile convulsions
- Seizures associated with poisoning and drug withdrawal
- Adjunct in acute alcohol withdrawal
- Premedication before major or minor surgery
- Sedation with amnesia for endoscopic procedures and surgery under local anesthesia
- In combination with pethidine, when anesthetic not available, for emergency reduction of fractures (Section 1.3)

- Anxiety disorders (Section 24.3)
- **Contraindications**
 - Respiratory depression
 - Acute pulmonary insufficiency
 - Sleep apnea
 - Severe hepatic impairment
 - Myasthenia gravis
 - In neonates avoid injections containing benzyl alcohol
- **Precautions**
 - Respiratory disease
 - Muscle weakness, history of alcohol or drug abuse, marked personality disorder
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Reduce dose in the elderly or debilitated patients and in hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Avoid prolonged use and abrupt withdrawal.
 - When given intravenously, facilities for reversing respiratory depression with mechanical ventilation must be at hand.
 - Porphyria
 - **Interactions:** Appendix A
 - **Skilled tasks:** May impair ability to perform skilled tasks (for example, operating machinery or driving. *See also* introductory notes to Section 5, above.

- **Dose**

Status epilepticus, emergency management of recurrent epileptic seizures, by slow intravenous injection (at a rate of 5 mg/min)

- **ADULT:** 10–20 mg, repeated if necessary after 30–60 minutes; may be followed by intravenous infusion up to a maximum of 3 mg/kg over 24 hours
- **CHILD:** 200–300 micrograms/kg (or 1mg per year of age)

Febrile convulsions (preferred treatment), by rectum

- **CHILD** over 10 kg: 500 micrograms/kg (max. 10 mg) with dose repeated if necessary

Febrile convulsions (alternative treatment), by slow intravenous injection

- **CHILD:** 200–300 micrograms/kg (or 1 mg per year of age)

Drug or alcohol withdrawal, by slow intravenous injection (at a rate of 5 mg/min)

- **ADULT:** 10 mg; higher doses may be required depending on severity of symptoms

Seizures associated with poisoning, by slow intravenous injection (at a rate of 5 mg/min)

- **ADULT:** 10–20 mg

Administration: Absorption following intramuscular injection is slow and erratic; this route should only be used if other routes—oral, rectal, or intravenous administration—are not possible. Slow intravenous injection into a large vein reduces risk of thrombophlebitis. Resuscitation equipment must be available.

Precautions for intravenous infusion: Intravenous infusion of diazepam is potentially hazardous (especially if prolonged), calling for close and constant observation, and is best carried out in a specialist center with intensive care facilities. Prolonged intravenous infusion may lead to accumulation and delay recovery.

- **Adverse effects**

- Drowsiness and light-headedness the next day
- Confusion and ataxia (especially in the elderly)
- Amnesia
- Dependence
- Paradoxical increase in aggression
- Muscle weakness
- Occasionally headache, vertigo, salivation changes, gastrointestinal disturbances, skin reactions, visual disturbances, dysarthria, tremor, changes in libido, incontinence, and urinary retention
- Blood disorders and jaundice
- Hypotension and apnea, pain and thrombophlebitis (with injection)

- **Ethosuximide**

Ethosuximide is a complementary anti-epileptic medicine.

- **Dosage form**

- Capsule: 250 mg
- Oral liquid: 250 mg/5 ml

- **Uses**

- Absence seizures

- **Precautions**

- Hepatic or renal impairment (blood counts and hepatic and renal function tests recommended)
- Pregnancy (*see note above*): Appendix B
- Breast-feeding (*see note above*): Appendix C
- Avoid sudden withdrawal (*see introductory notes to Section 5, above*)
- Porphyria
- **Interactions:** Appendix A
- **Blood disorders:** Patients or their carers should be told how to recognize signs of blood disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising or bleeding develop.
- **Skilled tasks:** May impair ability to perform skilled tasks (for example, operating machinery or driving). *See also* introductory notes to Section 5, above.

- **Dose**

Absence seizures, by mouth

- **ADULT and CHILD** over 6 years: Initially 500 mg daily, increased by 250 mg at intervals of 4–7 days to a usual maintenance dose of 1–1.5 g daily (in some cases, up to 2 g daily may be needed)
- **CHILD** under 6 years: Initially 250 mg daily, increased gradually to usual maintenance dose of 20 mg/kg daily

Patient advice: Daily doses of 1g and above should be taken as 2 or more divided doses.

Note: Plasma concentration for optimum response, 40–100 mg/L (300–700 micromole/l)

- **Adverse effects**

- Gastrointestinal disturbances including anorexia, hiccups, nausea and vomiting, and epigastric pain (particularly during initial treatment)
- Weight loss, drowsiness, dizziness, ataxia, headache, depression, mild euphoria
- Rarely rash including Stevens-Johnson syndrome (erythema multiforme), systemic lupus erythematosus, disturbances of liver and renal function (*see* Precautions), and hematological disorders (including leukopenia, agranulocytosis, aplastic anemia, thrombocytopenia, pancytopenia)
- Gum hyperplasia, swelling of tongue, irritability, hyperactivity, sleep disturbances, night terrors, aggressiveness, psychosis, increased libido, myopia, and vaginal bleeding also reported

- **Magnesium sulfate**

- **Dosage form**

- Injection: 500 mg/ml in 2 ml, 10 ml, and 20 ml ampoules

- **Uses**

- Prevention of recurrent seizures in eclampsia
- Prevention of seizures in pre-eclampsia

- **Precautions**

- *See* introductory notes to Section 5 above.

- Myasthenia gravis
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix B
- ***Interactions:*** Appendix A
- **Dose**

Prevention of recurrent seizures in eclampsia, by intravenous injection

- **ADULT and ADOLESCENT:** Initially 4 g over 5–15 minutes followed either *by intravenous infusion, 1 g/hour for at least 24 hours after the last seizure or delivery (whichever occurs later) or by deep intramuscular 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 *intravenous injection* of 2 g (4 g if body weight over 70 kg).

Prevention of seizures in pre-eclampsia, by intravenous infusion

- **ADULT and ADOLESCENT:** Initially 4 g over 5–15 minutes followed either *by intravenous infusion, 1 g/hour for 24 hours or by deep intramuscular 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 intravenous injection* of 2 g.

Dilution and administration: According to manufacturer's directions. For intravenous injection, the concentration of magnesium sulfate should not exceed 20% (dilute 1 part of magnesium sulfate injection, 50%, with at least 1.5 parts of

water for injection); for intramuscular injection, mix magnesium sulfate injection, 50%, with 1 mL lidocaine injection, 2%.

- **Adverse effects**

- Generally those associated with hypermagnesemia including nausea, vomiting, thirst, flushing of skin, hypotension, arrhythmias, coma, respiratory depression, drowsiness, confusion, loss of tendon reflexes, and muscle weakness

- **Phenobarbital**

- **Dosage form**

- Injection: 50 mg/ml, 100 mg/ml, and 200 mg/ml* in 2 ml ampoules
- Tablets: 15 mg, 25 mg, 30 mg, 50 mg, and 100 mg
- Oral solution: 15 mg/5 ml*

- **Uses**

- Generalized tonic-clonic seizures
- Partial seizures
- Neonatal seizures
- Febrile convulsions
- Status epilepticus

- **Contraindications**

- Porphyria
- Absence seizures (less than 20 seconds)

- **Precautions**

- The elderly, debilitated, children (may cause behavioral changes)
- Impaired renal function: Appendix D

- Impaired hepatic function: Appendix E
- Respiratory depression (avoid if severe)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Avoid sudden withdrawal (*see* introductory notes to Section 5 above).
- **Interactions:** Appendix A
- **Skilled tasks:** May impair ability to perform skilled tasks (such as operating machinery or driving). *See also* introductory notes to Section 5 above.

○ **Dose**

Generalized tonic-clonic seizures, partial seizures, by mouth

- **ADULT:** 60–180 mg at night
- **CHILD:** Up to 8 mg/kg daily

Febrile convulsions, by mouth

- **CHILD:** Up to 8 mg/kg daily

Neonatal seizures, by intravenous injection (dilute injection 1:10 with water for injections)

- **NEONATE:** 5–10 mg/kg every 20–30 minutes up to plasma concentration of 40 mg/L

Status epilepticus, by intravenous injection (dilute injection 1:10 with water for injection)

- **ADULT:** 10 mg/kg at a rate of not more than 100 mg/min (up to a maximum total dose of 1 g)
- **CHILD:** 5–10 mg/kg at a rate of not more than 30 mg/min

Note: For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect. Plasma concentration for optimum response, 15–40 mg/L (65–170 micromole/L).

- **Adverse effects**

- Sedation, mental depression, ataxia, nystagmus
- Allergic skin reactions, including, rarely, exfoliative dermatitis, toxic epidermal necrolysis, and Stevens-Johnson syndrome (erythema multiforme)
- Paradoxical excitement, restlessness, and confusion in the elderly
- Irritability and hyperactivity in children
- Megaloblastic anemia (may be treated with folic acid)
- Osteomalacia
- Status epilepticus (on treatment withdrawal)
- Hypotension, shock, laryngospasm, and apnea (with intravenous injection)

- **Valproic acid**

- **Dosage form**

- Oral liquid: 250 mg/5 ml
- Tablets: 200 mg, 250 mg, and 500 mg (sodium valproate)

- **Uses**

- Generalized tonic-clonic seizures
- Partial seizures
- Atonic seizures
- Absence seizures
- Myoclonic seizures
- Acute mania (Section 24.2.2)

- **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; Appendix E)
- Ensure no undue potential for bleeding before starting, and also before major surgery or anticoagulant therapy.
- Renal impairment: Appendix D
- Pregnancy (increased risk of birth defects and neonatal bleeding): Appendix B
- Breast-feeding: Appendix C
- Systemic lupus erythematosus
- False-positive urine tests for ketones
- Avoid sudden withdrawal.
- **Interactions:** Appendix A
- **Blood or hepatic disorders:** Patients or their carers 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, edema, vomiting, abdominal pain, drowsiness, or jaundice, or if spontaneous bruising or bleeding develops.

- **Pancreatitis:** Patients or their carers 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.

- **Dose**

All forms of epilepsy, by mouth

- **ADULT** and **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)
- **CHILD** up to 20 kg: Initially 20 mg/kg daily in divided doses, may be increased provided plasma concentrations monitored (above 40 mg/kg daily also monitor clinical chemistry and hematological 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

Note: Plasma concentrations in therapeutic range of 40–100 mg/L (280–700 micromole/L) is not generally considered useful in assessing control, but higher levels are associated with increased incidence of adverse effects; indicator of compliance, dose change, or co-medication.

- **Adverse effects**

- Gastrointestinal irritation, nausea, increased appetite, and weight gain
- Hyperammonemia
- Ataxia, tremor

- Transient hair loss (regrowth may be curly)
- Edema, thrombocytopenia, inhibition of platelet aggregation
- Impaired hepatic function and rarely fatal hepatic failure (withdraw treatment immediately if malaise, weakness, lethargy, edema, abdominal pain, vomiting, anorexia, jaundice, drowsiness, or loss of seizure control; *see also* Note in Precautions)
- Sedation reported and also increased alertness
- Behavioral disturbances
- Rarely pancreatitis (measure plasma amylase if acute abdominal pain; *see also* Note in Precautions), extrapyramidal symptoms, blood disorders (leukopenia, pancytopenia, red cell hypoplasia, and fibrinogen reduction; *see also* Note in Precautions)
- Irregular periods, amenorrhea, gynecomastia
- Hearing loss
- Fanconi syndrome
- Dementia
- Toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme), vasculitis, hirsutism, and acne reported

SECTION 6: Anti-infective medicines

LML strengths and dosage forms are marked in italic with an asterisk.

6.1 ANTHELMINTICS

6.1.1 Intestinal anthelminthics

Cestode infections

Cestode infections (tapeworms) include intestinal taeniasis and cysticercosis, hymenolepiasis (dwarf tapeworm), diphyllbothriasis, and echinococcosis (hydatid disease). Cysticercosis is a systemic infection caused by the larval form (cysticercus) of *Taenia solium*.

Neurocysticercosis occurs when the infection involves the brain. In man, echinococcosis is due to the larval stage of *Echinococcus granulosus* or *E. multilocularis*. The larvae (oncospheres) develop by expansion (cystic echinococcosis), or by tumor-like infiltration (alveolar echinococcosis) in the liver, lungs, or other organs.

Diphyllbothriasis

In diphyllbothriasis, **niclosamide** or **praziquantel** in a single dose is highly effective.

Hydroxocobalamin and folic acid supplements may also be required.

Echinococcosis

In echinococcosis, surgery (or, if this is not possible, a technique such as “puncture-aspiration-injection-re-aspiration”) is the treatment of choice for operable cystic disease

due to *E. granulosus*, but chemotherapy with benzimidazoles, such as **albendazole** and **mebendazole**, may be of value as adjunctive therapy. Alveolar echinococcosis due to *E. multilocularis* requires both surgery and long-term treatment with either mebendazole or albendazole to inhibit spread of the infection.

In animal studies, albendazole and mebendazole have been found to be teratogenic. Although there is some evidence to suggest that the use of mebendazole in pregnancy is not associated with an increased incidence of adverse effects on the fetus, **neither mebendazole nor albendazole should be used during the first trimester of pregnancy to treat nematode infections. Both mebendazole and albendazole are contraindicated for the treatment of cestode infections in pregnancy.**

Hymenolepiasis

In hymenolepiasis, **praziquantel** tends to be more effective than **niclosamide**, although resistance to praziquantel has been reported. Repeated treatment may be necessary to cure intense infections or eliminate the parasite within a family group or institution.

Taeniasis

In taeniasis, **praziquantel** is well tolerated and extensively absorbed and kills adult intestinal taenia worms in a single dose. Praziquantel also kills *T. solium* cysticerci when taken for 14 days in high doses and can therefore be used to treat neurocysticercosis.

Intestinal nematode infections

Intestinal nematode infections include ascariasis, capillariasis, enterobiasis, hookworm infection, strongyloidiasis, trichostrongyliasis, and trichuriasis.

Ascariasis

Ascariasis is an infection, usually of the small intestine, caused by *Ascaris lumbricoides* (roundworm). Single doses of **levamisole** or **pyrantel** are effective; the broad-spectrum anthelmintics, **albendazole** and **mebendazole**, are also effective.

Enterobiasis

Enterobiasis is an infection of the large intestine caused by *Enterobius vermicularis* (pinworm, threadworm). All household members should be treated concurrently with a single dose of **albendazole**, **mebendazole**, or **pyrantel**. Since reinfection readily occurs, at least 1 further dose should be given 2–4 weeks later. Piperazine is also effective but must be taken regularly for at least 7 consecutive days.

Hookworm infections

Hookworm infections are caused by *Ancylostoma duodenale* (ancylostomiasis) and *Necator americanus* (necatoriasis); they are a major cause of iron-deficiency anemia in the tropics and sub-tropics. Ideally, all cases of hookworm infection should be treated. However, when this is impracticable, priority should be given to women in the second and third trimesters of pregnancy, children, and debilitated patients. In hookworm, broad-

spectrum anthelmintics are preferred, especially wherever other nematode infections are endemic. Both **albendazole** and **mebendazole** are effective.

In animal studies, albendazole and mebendazole have been found to be teratogenic. Although there is some evidence to suggest that the use of mebendazole in pregnancy is not associated with an increased incidence of adverse effects on the fetus, **neither mebendazole nor albendazole should be used during the first trimester of pregnancy to treat nematode infections. Both mebendazole and albendazole are contraindicated for the treatment of nematode infections in pregnancy.**

Levamisole is effective in the treatment of mixed roundworm and hookworm infections.

Pyrantel has been highly effective against hookworm in some community-based control programs, although several doses are often needed to eliminate *Necator americanus* infection. Patients with iron-deficiency anemia caused by hookworm infection require supplementary iron salts and should receive ferrous sulfate (200 mg iron daily for adults) for at least 3 months after a hemoglobin concentration of 12 g/100 ml is attained.

Strongyloidiasis

Strongyloidiasis is an infection of the small intestine caused by *Strongyloides stercoralis*.

All infected patients should be treated. **Albendazole**, 400 mg once or twice daily for 3 days, is well tolerated by both adults and children aged over 2 years and may eradicate up to 80% of infections. **Mebendazole** has also been used, but, to be effective, it must be administered for longer periods as it has a limited effect on larvae and hence in prevention of autoinfection.

Trichostrongyliasis

Trichostrongyliasis is an infection of the small intestine caused by *Trichostrongylus* spp.

In symptomatic trichostrongyliasis, a single dose of **pyrantel** (10 mg/kg) or **albendazole** (400 mg) is effective.

Trichuriasis

Trichuriasis is an infection of the large intestine caused by *Trichuris trichiura*

(whipworm). Chemotherapy is required whenever symptoms develop or when fecal samples are found to be heavily contaminated (up to 10,000 eggs per gram). A single dose of **albendazole** (400 mg) or **mebendazole** (500 mg) can be effective in mild-to-moderate infections; heavier infections require a 3-day course.

Albendazole and mebendazole contraindicated in pregnancy

In animal studies, albendazole and mebendazole have been found to be teratogenic. They are therefore contraindicated for the treatment of **cestode** infections in pregnancy; furthermore, pregnancy should be excluded before treatment with albendazole and patients should be advised to use non-hormonal contraception during, and for 1 month after, treatment.

- **Albendazole**

- **Dosage form**

- Tablets (chewable): 200 mg and 400 mg
 - Oral suspension: 200 mg/5 ml in 10 ml bottle

- **Uses**

- *Echinococcus multilocularis* and *E. granulosus* infections prior to surgery or not amenable to surgery
- Nematode infections including ascariasis, enterobiasis, hookworm infections, strongyloidiasis, trichostrongyliasis, trichuriasis

- **Contraindications**

- Pregnancy (see introductory note above): Appendix B

- **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) (see introductory note above)

- Breast-feeding: Appendix B

- **Interactions:** Appendix A

- **Dose**

Ascariasis, hookworm infections, enterobiasis, and trichostrongyliasis, by mouth

- **ADULT** and **CHILD** over 2 years: 400 mg as a single dose
- **CHILD** 12 months–2 years: 200 mg as a single dose

Trichuriasis, by mouth

- **ADULT** and **CHILD** over 2 years: 400 mg as a single dose (for moderate infections) or 400 mg daily for 3 days (severe infections)

- **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)

Strongyloidiasis, by mouth

- **ADULT** and **CHILD** over 2 years: 400 mg once or twice daily for 3 days

Cystic echinococcosis, by mouth

- **ADULT** over 60 kg: 800 mg daily in 2 divided doses for 28 days followed by 14 tablet-free days
- **ADULT** 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

Alveolar echinococcosis, by mouth

- **ADULT:** As for cystic echinococcosis, but treatment cycles may need to be continued for months or years

Neurocysticercosis, by mouth

- **ADULT** over 60 kg: 800 mg daily in 2 divided doses for 8–30 days
- **ADULT** less than 60 kg: 15 mg/kg daily in 2 divided doses (maximum daily dose, 800 mg) for 8–30 days

○ **Adverse effects**

- Gastrointestinal disturbances, headache, dizziness
- Increases in liver enzymes
- Reversible alopecia
- Rash

- Fever
- Leukopenia and rarely pancytopenia
- Allergic shock if cyst leakage
- Convulsions and meningism in cerebral disease

- **Furazolidone**

- **Dosage form**

- Tablet: 100 mg
- Oral suspension: 125 mg/5 ml

- **Uses**

- *Giardiasis*
- In the absence of other effective drugs it is also used in the treatment of cholera.
- In exceptional cases it is also used in gastrointestinal infections.

- **Contraindications**

- **CHILD** under 1 month. (**Note:** According to WHO, it is not recommended for children under 1 year old.)

- **Precautions**

- Patients with G6PD deficiency due to hemolytic anemia
- As it inhibits monoamine oxydase (MAO), it should not be advised together with other sympathetic stimulator drugs.
- **Interactions:** Appendix A

- **Dose**

Giardiasis, by mouth

- **ADULT:** 100 mg 4 times daily for 2–5 days or for some patients 7–10 days
- **CHILD** 12 months–2 years: 200 mg as a single dose

Cholera in the absence of other effective drugs or, by mouth

- **ADULT:** 100 mg 4 times daily for 3 days

Treatment of giardiasis and cholera

- **CHILD** over 1 month: 1.25–1.5 mg/kg 4 times daily for 2–5 days and may be extended for 7–10 days if required

- **Adverse effects**

- Gastrointestinal disturbances, fever, rash, headache
- May cause hemolysis in G6PDF deficiency
- Rarely hypersensitivity reaction

- **Mebendazole**

Mebendazole is a representative benzimidazole carbamate derivative anthelmintic. Various medicines can serve as alternatives.

- **Dosage form**

- Oral chewable tablet: 100 mg

- **Uses**

- *Echinococcus granulosus* and *E. multilocularis* infections prior to surgery or not amenable to surgery
- Nematode infections including ascariasis, enterobiasis, hookworm infections, and trichuriasis
- **Contraindications**

- **PREGNANCY** (*see also* introductory note above): Appendix B

- **Precautions**
 - Blood counts and liver function tests recommended with high-dose regimens
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A

- **Dose**

Cystic echinococcosis, alveolar echinococcosis, by mouth

- **ADULT:** 4.5 g daily 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, by mouth

- **ADULT** and **CHILD** over 1 year: 500 mg as a single dose or 100 mg twice daily for 3 days

Hookworm infections, trichuriasis, by mouth

- **ADULT** and **CHILD** over 1 year: 100 mg twice daily for 3 days; if eggs persist in the feces, second course after 3–4 weeks

- Alternatively (especially for mass treatment control programs), *by mouth*,
ADULT and **CHILD** over 1 year: 500 mg as a single dose

Enterobiasis, by mouth

- **ADULT** and **CHILD** over 2 years: 100 mg as a single dose, repeated after interval of 2–3 weeks; all household members over 2 years should be treated at the same time

Patient advice: Doses should be taken between meals.

- **Adverse effects**

- Gastrointestinal disturbances, headache, dizziness
- With high doses, allergic reactions, raised liver enzymes, alopecia, and bone marrow depression

- **Niclosamide**

- **Dosage form**

- Tablet (chewable): 500 mg

- **Uses**

- Cestode (*Taenia saginata*, *T. solium*, *Hymenolepis nana*, and *Diphyllobothrium latum*) infections

- **Precautions**

- Chronic constipation (restore regular bowel movement before treatment)
- Give anti-emetic before treatment.
- Not effective against larval worms

- Pregnancy: Appendix B

- **Dose**

T. saginata and Diphylobothrium latum infection, by mouth

- **ADULT** and **CHILD** over 6 years: 1 g as a single dose after a light breakfast, followed by 1 g 1 hour later; followed by a laxative after 2 hours
- **CHILD** under 2 years: 250 mg
- **CHILD** 2–6 years: 500 mg

Hymenolepis nana infection, by mouth

- **ADULT** and **CHILD** over 6 years: 2 g as a single dose on the first day, then 1 g daily for 6 days
- **CHILD** under 2 years: 500 mg on the first day, then 250 mg daily for 6 days
- **CHILD** 2–6 years: 1 g on the first day, then 500 mg daily for 6 days

Patient advice: Tablets should be chewed thoroughly (or crushed) before washing down with water.

- **Adverse effects**

- Nausea, retching, abdominal pain
- Light-headedness
- Pruritus

6.1.2 Antischistosomes and antitrepanematode medicine

Fluke infections

The fluke infections include intestinal flukes, liver flukes, and pulmonary flukes. The common liver fluke in Afghanistan is *Fasciola hepatica*.

Praziquantel has transformed the therapy of most fluke infections. Parasitological cure has been obtained in virtually all cases (with the exception of *Fasciola* infections) without significant adverse effect but it needs to be taken for several days in the treatment of *Paragonimus* infections.

6.2 ANTIBACTERIALS

Choice of a suitable antibacterial drug

Choice of an antibacterial drug is based on the identity of the likely pathogen and its antibacterial sensitivity, as well as consideration of various factors relating to the patient (for example, history of allergy, renal and hepatic function, immune status, severity of illness, ethnic origin, and age).

Before starting therapy

The following should be considered before starting antimicrobial therapy:

Viral infections should **not** be treated with antibacterials. However, antibacterials are occasionally helpful in controlling secondary bacterial infections (for example, acute necrotizing ulcerative gingivitis secondary to herpes simplex infection).

Where possible, samples should be taken for culture and sensitivity testing; “blind” antibacterial prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis.

Knowledge of **prevalent organisms** and their current sensitivity is of great help in choosing an antibacterial before bacteriological confirmation is available.

The **dose** of an antibacterial varies according to a number of factors, including age, weight, hepatic function, renal function, and severity of infection. The prescribing of the so-called “standard” dose in serious infections may result in failure of treatment; therefore it is important to prescribe a dose appropriate to the condition. An inadequate dose may also increase the likelihood of antibacterial resistance. On the other hand, for an antibacterial with a narrow margin between its toxic and therapeutic dose (for example, an aminoglycoside), it is equally important to avoid an excessive dose. In such cases, the concentration of the drug in the plasma may need to be monitored.

The **route** of administration of an antibacterial often depends on the severity of the infection. Life-threatening infections generally require intravenous therapy. **However, antibacterials that are well absorbed can be given by mouth even for some serious infections. Whenever possible, painful intramuscular injections should be avoided in children.**

Duration of therapy depends on the nature of the infection and the response to treatment. Courses should not be unduly prolonged because this encourages resistance; furthermore, prolonged therapy may lead to unwanted side effects and unnecessary expense. However, in certain infections, such as tuberculosis or chronic osteomyelitis, it is necessary to treat for prolonged periods. Conversely, a single dose of an antibacterial may be all that is required to cure uncomplicated urinary tract infections.

6.2.1 Beta-lactam medicines

Beta-lactam antibiotics, which include penicillins, cephalosporins, and carbapenems, share a common structure; they are bactericidal, their mechanism of action resulting from inhibition of peptidoglycan, a mucopeptide in bacterial cell walls.

Benzylopenicillin and **phenoxymethylpenicillin** are active against susceptible strains of gram-positive bacteria and gram-negative bacteria, spirochetes, and actinomycetes, but are inactivated by penicillinase and other beta-lactamases.

Benzathine benzylopenicillin and **procaine benzylopenicillin** are long-acting preparations that slowly release benzylopenicillin on injection. A range of penicillins with improved stability to gastric acid and penicillinases have been produced by substitution of the 6-amino position of 6-aminopenicillanic acid. **Cloxacillin** is an isoxazolyl penicillin that is resistant to staphylococcal penicillinase. Broad-spectrum penicillins such as **ampicillin** are acid-stable and active against gram-positive and gram-negative bacteria, but are inactivated by penicillinase. Beta-lactamase inhibitors such as **clavulanic acid** are often

necessary to provide activity against beta-lactamases produced by a wide range of both gram-negative and gram-positive bacteria.

Cefalosporins are classified by generation, with the first-generation agents having gram-positive and some gram-negative activity; the second-generation drugs have improved gram-negative activity, while the third-generation cefalosporins have a wider spectrum of activity. Although the latter may be less active against gram-positive bacteria than the first-generation drugs, they are active against gram-negative *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Carbapenems are semi-synthetic derivatives of *Streptomyces cattleya*. They have a broad spectrum of activity and are stable to most penicillinases. They should be reserved for severe infections that are resistant to other antibiotics.

Penicillins may cause encephalopathy due to cerebral irritation. This rare but serious adverse effect may occur with very high doses or in patients with severe renal failure.

Penicillins should not be given by intrathecal injection because they can cause encephalopathy, which may be fatal.

Hypersensitivity

The most important adverse effect of penicillins is hypersensitivity, which causes rash and, occasionally, anaphylaxis, which can be fatal. A careful history should be taken with regard to previous allergic reactions. If rash develops, another antimicrobial should be substituted. Allergic reactions to penicillins occur in 1–10% of exposed individuals, while anaphylactic reactions occur in less than 0.05% of treated patients. Individuals with

a history of anaphylaxis, urticaria, or rash immediately after penicillin administration are at risk of immediate hypersensitivity to a penicillin. **These individuals should not receive a penicillin, a cephalosporin, or any other beta-lactam antibiotic.** Patients who are allergic to one penicillin will be allergic to all penicillins because hypersensitivity is related to the basic penicillin structure; moreover, about 10% of penicillin-sensitive patients will be allergic to cephalosporins and other beta-lactams. Individuals with a history of a minor rash (a non-confluent rash restricted to a small area of the body) or a rash occurring more than 72 hours after penicillin administration are possibly not allergic to penicillin and in these individuals, a penicillin should not be withheld unnecessarily for a serious infection; however, the possibility of an allergic reaction should be borne in mind and facilities should be available for treating anaphylaxis.

Benzylpenicillin and phenoxymethylpenicillin

Benzylpenicillin remains an important and useful antibiotic but it is inactivated by bacterial beta-lactamases. It is effective for many streptococcal (including pneumococcal), gonococcal, and meningococcal infections, and also for anthrax, diphtheria, gas gangrene, leptospirosis, tetanus, and treatment of Lyme disease in children. Pneumococci, meningococci, and gonococci often have so much decreased sensitivity to penicillins that benzylpenicillin is now no longer the first choice for pneumococcal meningitis. Benzylpenicillin is given by injection as it is inactivated by gastric acid and absorption from the intestinal tract is low. Depot preparations are used when therapeutic concentrations need to be sustained for several hours. Both **benzathine benzylpenicillin** and **procaine benzylpenicillin** provide a tissue depot from which the

drug is slowly absorbed over a period of 12 hours to several days. They are the preferred choices for the treatment of syphilis or yaws. **Phenoxymethylpenicillin** is suitable for oral administration; it has a similar spectrum of activity to benzylpenicillin but is less effective. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable.

Amoxicilline with clavulanic acid, ampicillin, and cloxacillin

Amoxicilline has a similar spectrum of activity to ampicillin, and is also inactivated by penicillinases. However, it is better absorbed after oral administration than ampicillin, and higher plasma and tissue levels are achieved. Amoxicilline is preferred to ampicillin for the treatment of some infections, including otitis media and respiratory tract and urinary tract infections.

Ampicillin is active against certain gram-positive and gram-negative organisms. It is used to treat a wide range of infections, including otitis media, respiratory tract and urinary tract infections, and gonorrhea due to susceptible bacteria. However, ampicillin is inactivated by penicillinases, including those produced by *Staphylococcus aureus*, and by common gram-negative bacilli, such as *Escherichia coli*; many strains of *Hemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, and *Salmonella* and *Shigella* spp. are resistant. There are geographical variations in the incidence of resistance, and an awareness of local patterns of resistance is important. In some areas, oral use should be restricted to treatment of *Shigella* infections; the recommended regimen in such cases is 1 g every 6 hours for 7–10 days.

Clavulanic acid is a beta-lactamase inhibitor. It has no significant antibacterial activity but in combination with **amoxicilline** widens amoxicilline's spectrum of activity and allows its use against amoxicilline-resistant strains of bacteria. It is used in respiratory tract, genitourinary and abdominal infections, cellulitis, animal bites, and dental infections.

Cloxacillin is used to treat infections due to penicillinase-producing staphylococci, which are resistant to benzylpenicillin. It is acid-stable and may therefore be given by mouth as well as by injection.

These antibiotics may also be administered with an aminoglycoside to increase their spectrum of activity. The penicillin and the aminoglycoside should not be mixed before or during administration, because loss of aminoglycoside activity can occur on mixing.

Cefalosporins

Cefazolin is a first-generation cefalosporin. Cefazolin is active against gram-positive bacteria such as *Staphylococcus aureus* and *Streptococcus* spp. and gram-negative bacteria including *Escherichia coli* and *Klebsiella* spp. Cefazolin is used for surgical prophylaxis of infection in clean surgery where there is no inflammation present, and where the respiratory, alimentary, and genitourinary tracts are not entered. This would include herniorrhaphy, cardiac, vascular, neurological, orthopedic and breast surgery.

Cefazolin is also used for prophylaxis in surgery where contamination can be controlled—for example, in cesarean section and abdominal hysteroscopy.

Cefixime, ceftazidime, and ceftriaxone are third-generation cephalosporins. Cefixime is orally active and is used for the treatment of uncomplicated gonorrhea. Ceftriaxone is used for serious infections such as septicemia, pneumonia, and meningitis; it is used as a reserve antimicrobial to treat meningitis due to *Streptococcus pneumoniae* in some areas where penicillin resistance is found. Ceftazidime is active against *Pseudomonas aeruginosa* and other gram-negative bacteria; it is used in the treatment of *Pseudomonas* infections but in some countries its use is restricted to areas where gentamicin resistance is high.

Carbapenems

Imipenem is a broad-spectrum antibiotic. As it is partially inactivated by enzymatic activity in the kidney, it is administered with cilastatin, which inhibits the renal metabolism of imipenem. It is active against many aerobic and anaerobic gram-positive and gram-negative bacteria; in some areas it is kept in reserve for the treatment of infections due to *Acinetobacter* spp. and *P. aeruginosa*, which are often resistant to other, more usual treatments.

- **Amoxicilline**

- **Dosage form**

- Oral ingestion suspension: 125 mg/5 ml and 250 mg/5 ml
 - Tablets and capsules: 250 mg, 500 mg, and 1 g*
 - Vial: 500 mg and 1 g*

- **Uses**

- Urinary tract infections, upper respiratory tract infections, bronchitis
 - Pneumonia
 - Otitis media
 - Dental abscess and other oral infections
 - Osteomyelitis
 - Lyme disease
 - Endocarditis prophylaxis
 - Post-splenectomy prophylaxis
 - Gynecological infections
 - Gonorrhea
 - Anthrax
 - *Helicobacter pylori* eradication (Section 17.1)

- **Contraindications**

- Hypersensitivity to penicillins (see introductory note above)

- **Precautions**

- History of allergy to penicillins (see introductory note above)

- Renal impairment: Appendix D
- Erythematous rash common in glandular fever, cytomegalovirus infection, chronic lymphatic leukemia, and sometimes in HIV infection
- Maintain adequate hydration with high doses (risk of crystalluria)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A
- **Dose**

Infections due to sensitive organisms, by mouth

- **ADULT** and **CHILD** over 10 years: 250 mg every 8 hours, doubled in severe infections
- **CHILD** up to 10 years: 125 mg every 8 hours, doubled in severe infections

Severe or recurrent purulent respiratory tract infections, by mouth

- **ADULT:** 3 g every 12 hours

Pneumonia, by mouth

- **ADULT:** 0.5–1 g every 8 hours

Urinary tract infections (short course), by mouth

- **ADULT:** 3 g repeated once after 10–12 hours

Dental abscess (short course), by mouth

- **ADULT:** 3 g repeated once after 8 hours

Uncomplicated genital chlamydial infection, non-gonococcal urethritis, by mouth

- **ADULT:** 500 mg every 8 hours for 7 days

Gonorrhea (short course), by mouth

- **ADULT:** 3 g as a single dose (with probenecid, 1 g)

Otitis media, by mouth

- **ADULT:** 1 g every 8 hours
- **CHILD:** 40 mg/kg daily in 3 divided doses (maximum 3 g daily)

- **Adverse effects**

- Nausea and vomiting, diarrhea
- Rash (hypersensitivity or toxic response; may be indicative of a serious reaction—discontinue treatment)
- Hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness–like reactions, hemolytic anemia, and interstitial nephritis (*see also* introductory note above)
- Rarely antibiotic-associated colitis
- Neutropenia, thrombocytopenia, coagulation disorders
- Rarely central nervous system disorders including convulsions (associated with high doses or impaired renal function)

- **Amoxicilline + clavulanic acid**

- **Dosage form**

- Tablets: 500 mg + 125 mg, 875 mg + 125 mg,* 250 mg + 125 mg*
- Oral ingestion suspension: 125 mg + 31.25 mg per 5 ml, 200 mg + 28.5 mg per 5 ml,* 250 mg + 62.5 mg per 5 ml*

- *Injection powder: 1 g amoxicilline (as sodium salts) + 200 mg clavulanic acid (as potassium salt)**

- **Uses**

- Infections due to beta-lactamase-producing bacteria (where amoxicilline alone is not appropriate) including respiratory tract infections, otitis media, genitourinary and abdominal infections, cellulitis, animal bites, severe dental infections, *Hemophilus influenzae* osteomyelitis, and surgical prophylaxis

- **Contraindications**

- Hypersensitivity to penicillins (*see* introductory note above); history of penicillin- or amoxicilline with clavulanic acid–associated jaundice or hepatic dysfunction

- **Precautions**

- History of allergy to penicillins (*see* introductory note above)
- Renal impairment: Appendix D
- Erythematous rash (common in glandular fever, cytomegalovirus infection), chronic lymphatic leukemia, and possibly HIV infection
- Maintain adequate hydration with high doses (risk of crystalluria)
- Hepatic impairment: Appendix E
- Pregnancy: Appendix B

- Breast-feeding: Appendix C
- **Interactions:** Appendix A

○ **Dose**

Note: All doses expressed as amoxicilline

Infections due to susceptible beta-lactamase-producing organisms, by mouth

- **ADULT** and **CHILD** over 12 years: 250 mg every 8 hours, doubled in severe infections
- **CHILD** under 1 year: 20 mg/kg daily in 3 divided doses
- **CHILD** 1–6 years: 125 mg every 8 hours
- **CHILD** 6–12 years: 250 mg every 8 hour

Severe dental infections, by mouth

- **ADULT:** 250 mg every 8 hours for 5 days

Infections due to susceptible beta-lactamase-producing organisms, by intravenous injection over 3–4 minutes

- **ADULT** and **CHILD** over 12 years: 1 g every 8 hours, increased to 1 g every 6 hours in severe infections
- **NEONATE** and **PREMATURE INFANT:** 25 mg/kg every 12 hours
- **INFANT** up to 3 months: 25 mg/kg every 8 hours
- **CHILD** 3 months–12 years: 25 mg/kg every 8 hours, increased to 25 mg/kg every 6 hours in more severe infections

Surgical prophylaxis, by intravenous injection

- **ADULT:** 1 g at induction, with up to 2–3 further doses of 1 g every 8 hours if increased risk of infection

Reconstitution and administration: According to manufacturer's directions

○ **Adverse effects**

- Nausea and vomiting, diarrhea
- Rash (hypersensitivity or toxic response; may be indicative of a serious reaction—discontinue treatment)
- Hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness–type reactions, hemolytic anemia, and interstitial nephritis (*see also* introductory note above)
- Rarely antibiotic-associated colitis
- Neutropenia, thrombocytopenia, coagulation disorders
- Dizziness, headache, convulsions (particularly with high doses or in renal impairment)
- Hepatitis, cholestatic jaundice
- Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and vasculitis reported
- Superficial staining of teeth with suspension
- Phlebitis at injection site

- **Ampicillin**

- **Dosage form**

- Capsule: 250 mg and 500 mg
 - Oral suspension: 125 mg and 250 mg/5 ml
 - Injection powder: 500 mg and 1 g per vial (as sodium salts)

- **Uses**

- Mastoiditis
 - Gynecological infections
 - Septicemia
 - Peritonitis
 - Endocarditis
 - Meningitis
 - Cholecystitis
 - Osteomyelitis

- **Contraindications**

- Hypersensitivity to penicillins (*see* introductory note above)

- **Precautions**

- History of allergy (*see* introductory note above)
 - Renal impairment: Appendix D

- Erythematous rash (common in glandular fever, acute or chronic lymphatic leukemia, and cytomegalovirus infection)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

○ **Dose**

Severe infections due to sensitive organisms, by intramuscular injection, by slow intravenous injection or by intravenous infusion

- **ADULT:** 500 mg every 4–6 hours
- **CHILD** under 10 years: One-half the adult dose

Meningitis, by slow intravenous injection

- **ADULT:** 1–2 g every 3–6 hours (maximum 14 g daily)
- **CHILD:** 150–200 mg/kg daily in divided doses

Listerial meningitis (in combination with another antibacterial), by intravenous infusion

- **ADULT:** 12 g daily in divided doses every 4–6 hours for 10–14 days
- **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)

Reconstitution and administration: According to manufacturer's directions

- **Adverse effects**

- Nausea and vomiting, diarrhea
- Rash (hypersensitivity or toxic response; may be indicative of a serious reaction—discontinue treatment)
- Hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness–like reactions, hemolytic anemia, and interstitial nephritis (*see also* introductory note above)
- Rarely antibiotic-associated colitis
- Neutropenia, thrombocytopenia, coagulation disorders

- **Benzathine benzylpenicillin**

- **Dosage form**

- Powder for injection: 1.44 g benzylpenicillin (= 2.4 million IU) and 0.72 g benzylpenicillin (= 1.2 million IU)

- **Uses**

- Streptococcal pharyngitis
- Diphtheria
- Syphilis and other treponemal infections
- Rheumatic fever prophylaxis

- **Contraindications**

- Hypersensitivity to penicillins (*see* introductory note above)
- Intravascular injection
- Neurosyphilis

- **Precautions**

- History of allergy to penicillins (*see* introductory note above)
- Renal failure: Appendix D
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Dose**

Streptococcal pharyngitis; primary prophylaxis of rheumatic fever, by deep intramuscular injection

- **ADULT** and **CHILD** over 30 kg: 900 mg as a single dose
- **CHILD** under 30 kg: 450–675 mg as a single dose

Secondary prophylaxis of rheumatic fever, by deep intramuscular injection

- **ADULT** and **CHILD** over 30 kg: 900 mg once every 3–4 weeks
- **CHILD** under 30 kg: 450 mg once every 3–4 weeks

Early syphilis, by deep intramuscular injection

- **ADULT:** 1.8 g as a single dose, divided between 2 sites

Late syphilis, by deep intramuscular injection

- **ADULT:** 1.8 g, divided between 2 sites, once weekly for 3 consecutive weeks

Congenital syphilis (where no evidence of CSF involvement), by deep intramuscular injection

- **CHILD** up to 2 years: 37.5 mg/kg as a single dose

Reconstitution and administration: According to manufacturer's directions

- **Adverse effects**

- See under procaine benzylpenicillin

- **Benzylpenicillin (penicillin G)**

- **Dosage form**

- Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU)
(sodium or potassium salt) in vial

- **Uses**

- Pneumonia
- Throat infections
- Otitis media

- Lyme disease
- Streptococcal endocarditis
- Meningococcal disease
- Necrotizing enterocolitis
- Necrotizing fasciitis
- Leptospirosis
- Neurosyphilis
- Anthrax
- Relapsing fever
- Actinomycosis
- Brain abscess
- Gas gangrene
- Cellulitis
- Osteomyelitis

- **Contraindications**

- Hypersensitivity to penicillins (*see* introductory note above)
- Avoid intrathecal route (*see* introductory note above)

- **Precautions**

- History of allergy to penicillins (*see* introductory note above)
- Renal failure: Appendix D
- Heart failure

- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

Note: When penicillin is mixed with distilled water, it should be used within 24 hours—otherwise its efficacy will be reduced.

○ **Dose**

Mild-to-moderate infections due to sensitive organisms, by intramuscular injection, by slow intravenous injection or by intravenous infusion

- **ADULT:** 2.4–4.8 g daily in 4 divided doses, with higher doses in severe infections
- **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

Bacterial endocarditis, by slow intravenous injection or by intravenous infusion

- **ADULT:** 7.2–14.4 g daily in 6 divided doses

Meningococcal disease, by slow intravenous injection or by intravenous infusion

- **ADULT:** Up to 14.4 g daily in divided doses

- **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 transfer to hospital), by intramuscular injection or by slow intravenous injection*
- **ADULT** and **CHILD** over 10 years: 1.2 g
 - **INFANT** under 1 year: 300 mg
 - **CHILD** 1–9 years: 600 mg

Neurosyphilis, by slow intravenous injection

- **ADULT:** 1.8–2.4 g every 4 hours for 2 weeks

Congenital syphilis, by slow intravenous 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

Congenital syphilis, by intramuscular injection or slow intravenous injection

- **CHILD** over 2 years, 120–180 mg/kg (max. 1.44 g) daily in 4–6 divided doses for 10–14 days

Reconstitution and administration: According to manufacturer's directions.

Intravenous route preferred for neonates and infants; doses over 1.2 g should be given by the intravenous route only.

- **Adverse effects**

- Hypersensitivity reactions including urticaria, fever, joint pains, rash, angioedema, anaphylaxis, serum sickness–like reactions, hemolytic anemia, and interstitial nephritis (*see also* introductory notes above)
- Diarrhea, antibiotic-associated colitis
- Neutropenia, thrombocytopenia, coagulation disorders
- Central nervous system 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 spirochete infections, probably due to release of endotoxins)
- Inflammation, phlebitis, or thrombophlebitis at injection sites

- **Procaine benzylpenicillin**

- **Dosage form**

- Powder for injection: 1 g (= 1 million IU); 2 g (= 2 million IU); 4 g (= 4 million IU) in vial

- **Uses**

- Syphilis
- Anthrax
- Pneumonia

- Diphtheria
- Cellulitis
- Mouth infections
- Animal bites
- **Contraindications**
 - Hypersensitivity to penicillins (*see* introductory note above)
 - Intravascular injection
- **Precautions**
 - History of allergy to penicillins (*see* introductory note above)
 - Renal failure: Appendix D
 - Breast-feeding: Appendix C
 - ***Interactions:*** Appendix A
- **Dose**

Infections due to sensitive organisms, by deep intramuscular injection

- **ADULT:** 0.6–1.2 g daily

Pneumonia, by deep intramuscular injection

- **CHILD:** 50 mg/kg daily for 10 days

Syphilis, by deep intramuscular injection

- **ADULT:** 1.2 g daily for 10–15 days, or up to 3 weeks in late syphilis

Neurosyphilis, by deep intramuscular injection

- **ADULT:** 1.2 g daily (together with probenecid, 500 mg 4 times daily by mouth) for 10–14 days

Congenital syphilis, by deep intramuscular injection

- **CHILD** up to 2 years: 50 mg/kg daily for 10 days

Reconstitution and administration: According to manufacturer's directions

- **Adverse effects**

- Hypersensitivity reactions including urticaria, fever, joint pains, rash, angioedema, anaphylaxis, serum sickness–like reactions, hemolytic anemia, and interstitial nephritis (*see also* introductory note above)
- Neutropenia, thrombocytopenia, coagulation disorders, and central nervous system toxicity (associated with high doses and severe renal failure)
- Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochete infections, probably due to release of endotoxins)
- Rarely non-allergic (embolic-toxic) reactions
- Pain and inflammation at injection site

- **Phenoxymethylpenicillin / penicillin V**

- **Dosage form**

- Tablets: 250 mg and 500 mg (as potassium salt)

- Powder for oral liquid: 250 mg (as potassium salt)/5 ml

- **Uses**

- Streptococcal pharyngitis
- Otitis media
- Cellulitis
- Mouth infections
- Secondary prophylaxis of rheumatic fever
- Post-splenectomy prophylaxis

- **Contraindications**

- Hypersensitivity to penicillins (*see* introductory note above)
- Serious infections (*see* introductory note above)

- **Precautions**

- History of allergy to penicillins (*see* introductory note above)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- ***Interactions:*** Appendix A

- **Dose**

Infections due to sensitive organisms, by mouth

- **ADULT:** 500 mg every 6 hours increased up to 1 g every 6 hours in severe infections
- **CHILD** up to 1 year: 62.5 mg every 6 hours
- **CHILD** 1–5 years: 125 mg every 6 hours
- **CHILD** 6–12 years: 250 mg every 6 hours

Secondary prophylaxis of rheumatic fever, by mouth

- **ADULT:** 500 mg twice daily
- **CHILD** 1–5 years: 125 mg twice daily
- **CHILD** 6–12 years: 250 mg twice daily

Patient advice: Phenoxymethylpenicillin should be taken at least 30 minutes before, or 2 hours after, food.

- **Adverse effects**

- Hypersensitivity reactions including urticaria, joint pain, rash, angioedema, and anaphylaxis (*see also* introductory note above)
- Nausea and diarrhea

- **Ceftriaxone**

Ceftriaxone is a representative third-generation cephalosporin antibiotic. Various medicines can serve as alternatives.

- **Dosage form**

- Powder for injection: 250 mg, 500 mg, 1 g, and 2 g per vial (as sodium salt)

- **Uses**

- Serious infections due to sensitive bacteria, including septicemia, pneumonia, and meningitis
- Osteomyelitis, septic arthritis
- *Hemophilus influenzae* epiglottitis
- Surgical prophylaxis
- Prophylaxis of meningococcal meningitis
- Shigellosis
- Invasive salmonellosis
- Endocarditis
- Gonococcal conjunctivitis
- Gonorrhea
- Pelvic inflammatory disease
- Lyme disease

- **Contraindications**

- Hypersensitivity to cephalosporins
- Porphyria
- Neonates with jaundice, hypoalbuminemia, acidosis, or impaired bilirubin binding

- **Precautions**

- Sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reactions; *see* introductory note above)
- Severe renal impairment: Appendix D
- Hepatic impairment if accompanied by renal impairment: Appendix E
- Premature neonates (may displace bilirubin from serum albumin)
- Treatment longer than 14 days, renal failure, dehydration, or concomitant total parenteral nutrition (risk of ceftriaxone precipitation in gallbladder)
- Pregnancy and breast-feeding (but appropriate to use, *see* Appendices B and C)
- False-positive urinary glucose (if tested for reducing substances) and false-positive Coombs' test
- **Interactions:** Appendix A

- **Dose**

Infections due to susceptible organisms, by deep intramuscular injection, by intravenous injection (over at least 2–4 minutes), or by intravenous infusion

- **ADULT:** 1 g daily; up to 2–4 g daily in severe infections

- **INFANT** and **CHILD** under 50 kg: 20–50 mg/kg daily should be given, up to 80 mg/kg daily in severe infections (doses of 50 mg/kg and over by intravenous infusion only)
- **NEONATE:** 20–50 mg/kg daily *by intravenous infusion* (over 60 minutes) (max. 50 mg/kg daily)

Uncomplicated gonorrhea and gonococcal conjunctivitis, by deep intramuscular injection

- **ADULT:** 125 mg as a single dose (also used with doxycycline and metronidazole to treat pelvic inflammatory disease)

Neonatal gonococcal conjunctivitis, by intramuscular injection

- **NEONATE:** 50 mg/kg as a single dose (max. 125 mg)

Disseminated gonococcal infection, by deep intramuscular injection or by intravenous injection

- **ADULT:** 1 g daily for 7 days

Surgical prophylaxis, by deep intramuscular injection or by intravenous injection (over at least 2–4 minutes)

- **ADULT:** 1 g at induction

Colorectal surgery (with an antibacterial active against anaerobes), by deep intramuscular injection, by intravenous injection (over at least 2–4 minutes), or by intravenous infusion

- **ADULT:** 2 g as a single dose

Reconstitution and administration: According to manufacturer's directions.

Intramuscular doses over 1 g should be divided between more than one site.

Administer by intravenous infusion over 60 minutes in neonates (*see also*

Contraindications).

○ **Adverse effects**

- Diarrhea, 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 anemia, and hemolytic anemia)
- 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 those who are immobilized) or in the gallbladder (consider discontinuation if symptomatic)
- Rarely prolongation of prothrombin time and pancreatitis

- **Cloxacillin**

Cloxacillin is a representative penicillinase-resistant penicillin. Various medicines (such as dicloxacillin) can serve as alternatives.

- **Dosage form**

- Capsules: 250 mg and 500 mg
- Oral suspension: 125 mg/5 ml and 250 mg/5 ml, in 100 ml bottles
- Injection powder: 500 mg per vial

- **Uses**

- Infections due to beta-lactamase-producing staphylococci including impetigo, cellulitis, and other soft-tissue infections
- Pyomyositis
- Staphylococcal endocarditis, septicemia, pneumonia, septic arthritis, and osteomyelitis
- Otitis externa

- **Contraindications**

- Hypersensitivity to penicillins (*see* introductory note above)

- **Precautions**

- History of allergy to penicillins (*see* introductory note above)
- Renal impairment: Appendix D

- Hepatic impairment: Appendix E
- Heart failure
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- ***Interactions:*** Appendix A

○ **Dose**

Infections due to susceptible beta-lactamase-producing staphylococci

- **ADULT**, *by mouth*: 500 mg 4 times daily, doubled in severe infection
- **ADULT**, *by intramuscular injection*: 250 mg every 4–6 hours, doubled in severe infection
- **ADULT**, *by slow intravenous injection or by intravenous infusion*: 1–2 g every 6 hours
- **CHILD** up to 2 years: One-quarter the adult dose
- **CHILD** 2–10 years: One-half half the adult dose

Reconstitution and administration: According to manufacturer's directions

○ **Adverse effects**

- Nausea and vomiting, diarrhea

- Hypersensitivity reactions including urticaria, fever, joint pain, rash, angioedema, anaphylaxis, serum sickness–like reactions, hemolytic anemia, and interstitial nephritis (*see also* introductory note above)
- Neutropenia, thrombocytopenia, coagulation disorders
- Rarely antibiotic-associated colitis; hepatitis and cholestatic jaundice (may be delayed in onset); electrolyte disturbances; pain, inflammation, phlebitis, or thrombophlebitis at injection sites

6.2.2 Other antibacterial medicines

- **Azithromycin**

- **Dosage form**

- Capsules: 250 mg and 500 mg (as dihydrate)
 - Oral liquid: 200 mg/5 ml (as dihydrate)

Azithromycin is more active than erythromycin against some gram-negative organisms, such as *Chlamydia trachomatis*. The concentration and persistence of azithromycin is much higher in tissue than in plasma. A single dose of azithromycin is recommended for use in the treatment of uncomplicated genital chlamydia and trachoma, but it is not recommended if there is a possibility of gonorrhea because macrolide resistance emerges rapidly when it is used under these circumstances.

- **Uses**

- Uncomplicated genital chlamydial infections and trachoma
- **Contraindications**
 - Hepatic impairment: Appendix E
- **Precautions**
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Prolongation of QT interval (ventricular tachycardia reported)
 - ***Interactions:*** Appendix A
- **Dose**

Uncomplicated genital chlamydial infections, trachoma, by mouth

- **ADULT** over 45 kg: 1 g as a single dose
- **ADULT** under 45 kg: 20 mg/kg as a single dose

Patient advice: 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.

- **Adverse effects**
 - *See under* Erythromycin (but fewer gastrointestinal effects)

- Anorexia, dyspepsia, flatulence, constipation, pancreatitis
- Syncope, dizziness, headache, drowsiness, agitation, anxiety, hyperactivity
- Photosensitivity
- Hepatitis, interstitial nephritis, acute renal failure, asthenia, paresthesia, arthralgia, convulsions, mild neutropenia, thrombocytopenia, tinnitus, hepatic necrosis, hepatic failure, tongue discoloration, and taste disturbances

- **Chloramphenicol**

Chloramphenicol is a potent broad-spectrum antibiotic. However, it is associated with serious hematological adverse effects and should be reserved for the treatment of severe infections, particularly those caused by *Hemophilus influenzae* and typhoid fever. The oily suspension should be reserved for use in situations of catastrophic epidemics of meningococcal meningitis, such as those that occur in sub-Saharan Africa, in which the scale of the epidemic often overwhelms the medical services and precludes any other form of antimicrobial therapy.

- **Dosage form**

- Capsule: 250 mg
- Oral liquid: 125 mg (as palmitate)/5 ml
- Powder for injection: 500 mg and 1 g (sodium succinate) in vial

- **Uses**

- Severe life-threatening infections, particularly those caused by *Hemophilus influenzae* and typhoid fever
- Pneumonia
- Cerebral abscess
- Mastoiditis
- Rickettsia
- Relapsing fever
- Gangrene
- Granuloma inguinale
- Listeriosis
- Plague
- Psitticosis
- Tularemia
- Whipple disease
- Septicemia
- Meningitis

○ **Contraindications**

- Pregnancy: Appendix B
- Porphyria

○ **Precautions**

- Avoid repeated courses and prolonged use.

- Hepatic impairment (reduce dose): Appendix E
- Severe renal impairment (reduce dose): Appendix D
- Blood count required before and during treatment
- Monitor plasma concentrations in neonates (*see below*)
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

○ **Dose**

Infections due to susceptible organisms that are not susceptible to other antimicrobials, by mouth, by intravenous injection, or by intravenous infusion

- **ADULT** and **CHILD:** 50 mg/kg daily in 4 divided doses; up to 100 mg/kg daily in divided doses in severe infections such as meningitis, septicemia, and *Hemophilus epiglottitis* (reduce high doses as soon as clinically indicated)
- **NEONATE** under 2 weeks: 25 mg/kg daily in 4 divided doses
- **INFANT** 2 weeks to 1 year: 50 mg/kg daily in 4 divided doses

Epidemics of meningococcal meningitis, by intramuscular injection (of oily suspension)

- **ADULT:** 3 g as a single dose, repeated after 48 hours if necessary
- **INFANT** 1–8 weeks: 250 mg as a single dose
- **INFANT** 2–11 months: 500 mg as a single dose
- **CHILD** 1–2 years: 1 g as a single dose

- **CHILD** 3–5 years: 1.5 g as a single dose
- **CHILD** 6–9 years: 2 g as a single dose
- **CHILD** 10–14 years: 2.5 g as a single dose
- **CHILD** over 15 years: As for adult, repeated after 48 hours if necessary

Reconstitution and administration: According to manufacturer’s directions.

The oily suspension is for intramuscular use only.

Note: Plasma concentration monitoring is required in neonates and is preferred in those under 4 years of age, in the elderly, and in hepatic impairment; recommended peak plasma chloramphenicol concentration (measured approximately 1 hour after intravenous injection or infusion) is 15–25 mg/L; pre-dose “trough” concentration should not exceed 15 mg/L.

○ **Adverse effects**

- Bone marrow depression—reversible and irreversible aplastic anemia (with reports of leukemia), anemia, leukopenia, and thrombocytopenia
- Nocturnal hemoglobinuria
- Peripheral neuritis and optic neuritis
- Nausea, vomiting, diarrhea, dry mouth, stomatitis, glossitis
- Headache, depression
- Hypersensitivity reactions including rash, urticaria, fever, angioedema, and rarely anaphylaxis

- Grey syndrome (vomiting, greenish diarrhea, abdominal distension, hypothermia, pallid cyanosis, irregular respiration, circulatory collapse) may follow excessive doses in neonates with immature hepatic metabolism.
- Grey syndrome also reported in infants born to mothers treated in late pregnancy

- **Ciprofloxacin**

Ciprofloxacin is a representative quinolone antibacterial. Various medicines can serve as alternatives.

Ciprofloxacin is active against both gram-positive and gram-negative bacteria. It is particularly active against salmonella, shigella, campylobacter, Neisseria, *Bacillus anthracis*, and *Pseudomonas* ssp. It is also active against chlamydia and some mycobacteria. Most anaerobic organisms are, however, not susceptible. Ciprofloxacin is used with doxycycline and metronidazole to treat pelvic inflammatory disease.

- **Dosage form**

- Tablets: 100 mg, 250 mg, 500 mg, and 750 mg (as hydrochloride)
- Infusion solution: 2 mg/ml in 50 ml, and 100 ml
- Oral syrup: 125 and 250 mg in 5 ml

- **Uses**

- Gastroenteritis (including cholera, shigellosis, travelers' diarrhea, campylobacter, and salmonella enteritis)
- Typhoid
- Gonorrhea
- Chancroid
- Pelvic inflammatory disease (with doxycycline and metronidazole)
- Legionnaires' disease
- Meningitis (including meningococcal meningitis prophylaxis)
- Respiratory tract infections (including pseudomonal infections in cystic fibrosis, but not pneumococcal pneumonia)
- Urinary tract infections
- Bone and joint infections
- Septicemia
- Anthrax skin infections
- Otitis externa
- Prophylaxis in surgery
- Eye infections (Section 21.1)

- **Contraindications**

- History of tendon disorders related to quinolone use

- **Precautions**

- History of epilepsy or conditions that predispose to seizures, G6PD deficiency, myasthenia gravis (risk of exacerbation)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Children or adolescents (*see note below*)
- Avoid exposure to excessive sunlight (discontinue if photosensitivity occurs)
- Rarely tendon damage (*see note below*)
- Renal impairment: Appendix D
- Avoid excessive alkalinity of urine and ensure adequate fluid intake (risk of crystalluria)
- ***Interactions:*** Appendix A

Use in children: Ciprofloxacin causes arthropathy in the weight-bearing joints of immature animals and is 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 of ciprofloxacin in children may be justified. For example, ciprofloxacin is used to treat pseudomonal infections in cystic fibrosis (for children over 5 years), and for treatment and prophylaxis of inhalational anthrax.

Tendon damage: 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 tendinitis.
- ➔ The risk of tendon rupture is increased by the concomitant use of corticosteroids.
- ➔ If tendinitis is suspected, the quinolone should be discontinued immediately.

Skilled tasks: Warn patient not to perform skilled tasks (such as operating machinery or driving) for 24 hours.

○ **Dose**

Infections due to susceptible organisms, by mouth

- **ADULT:** 250–750 mg twice daily

Shigellosis, by mouth

- **ADULT:** 500 mg twice daily for 3 days

Cholera, by mouth

- **ADULT:** 1 g as a single dose

Acute uncomplicated cystitis, by mouth

- **ADULT:** 100 mg twice daily for 3 days

Gonorrhea and gonococcal conjunctivitis, by mouth

- **ADULT:** 500 mg as a single dose

Chancroid, by mouth

- **ADULT:** 500 mg twice daily for 3 days

Pelvic inflammatory disease, by mouth

- **ADULT:** 500 mg twice daily

Pseudomonal lower respiratory tract infection in cystic fibrosis, by mouth

- **ADULT:** 750 mg twice daily
- **CHILD** 5–17 years: (*see also* Precautions), up to 20 mg/kg twice daily (max. 1.5 g daily)

Surgical prophylaxis, by mouth

- **ADULT:** 750 mg, 60–90 minutes before procedure

Prophylaxis of meningococcal meningitis, by mouth

- **ADULT:** 500 mg as a single dose

○ **Adverse effects**

- Nausea, vomiting, dyspepsia, abdominal pain, flatulence, diarrhea (rarely antibiotic-associated colitis)
- Pancreatitis, dysphagia, tremor, hyperglycemia, headache, dizziness, sleep disorders, rash (rarely erythema multiforme [Stevens-Johnson syndrome] and toxic epidermal necrolysis), pruritus

- Vasculitis, erythema nodosum, petechiae, hemorrhagic bullae
- Less frequently anorexia and increased blood urea and creatinine
- Drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, paresthesia, hypoesthesia, movement disorders
- Photosensitivity, hypersensitivity reactions (including fever, urticaria, angioedema, arthralgia, myalgia, and anaphylaxis)
- Blood disorders (including eosinophilia, leukopenia, thrombocytopenia)
- Disturbances in vision, taste, hearing, and smell, tinnitus
- Tenosynovitis
- Tachycardia, hypotension, edema, syncope, hot flushes and sweating
- Also isolated reports of tendon inflammation and damage (especially in the elderly and in those taking corticosteroids; *see* also note above)
- Hemolytic anemia, renal failure, interstitial nephritis, and hepatic dysfunction (including hepatitis and cholestatic jaundice)
- Discontinue if psychiatric, neurological, or hypersensitivity reactions (including severe rash) occur.

- **Clindamycin**

Clindamycin is a bacteriostatic antibacterial with activity against gram-positive aerobes and a wide range of anaerobes. However, its use is limited because of adverse effects. Antibiotic-associated colitis can occur with a wide range of antibacterials, but occurs most frequently with clindamycin. It may be fatal and is most common in women and the elderly; it can develop during or after treatment.

Patients should discontinue treatment immediately if diarrhea develops.

Clindamycin is recommended for the treatment of staphylococcal bone and joint infections and for intra-abdominal sepsis. It is also used for endocarditis prophylaxis when penicillin is not appropriate. Clindamycin is a complementary list medicine for use when penicillin is not appropriate.

- **Dosage form**

- Capsules: 150 mg and 300 mg
- Injection: 950 mg in 50 ml dextrose (for infusion)

- **Uses**

- Staphylococcal bone and joint infections, pyomyositis
- Necrotizing fasciitis
- Peritonitis
- Endocarditis prophylaxis
- Pelvic inflammatory disease (with gentamicin)
- Pneumonia

- **Contraindications**

- Diarrheal states
- Avoid injections containing benzyl alcohol in neonates
- Porphyria

- **Precautions**

- Discontinue immediately if diarrhea or colitis develop
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Monitor liver and renal function on prolonged therapy and in neonates and infants
- Elderly
- Females
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Avoid rapid intravenous administration
- **Interactions:** Appendix A

- **Dose**

Osteomyelitis or peritonitis, by mouth

- **ADULT:** 150–300 mg every 6 hours, up to 450 mg every 6 hours in severe infections
- **CHILD:** 3–6 mg/kg every 6 hours

By deep intramuscular injection or by intravenous infusion

- **ADULT:** 0.6–2.7 g daily in 2–4 divided doses, increased up to 4.8 g daily in life-threatening infections (single doses over 600 mg should be given by intravenous infusion only; single doses given by intravenous infusion should not exceed 1.2 g)

- **NEONATE:** 15–20 mg/kg daily
- **CHILD** over 1 month: 15–40 mg/kg daily in 3–4 divided doses, increased to at least 300 mg daily, regardless of weight, in severe infections

Pelvic inflammatory disease, by intravenous infusion

- **ADULT:** 900 mg every 8 hours

Endocarditis prophylaxis (for procedures under local or no anesthetic), by mouth

- **ADULT:** 600 mg, 1 hour before procedure

Endocarditis prophylaxis (for procedures under general anesthetic), by intravenous infusion

- **ADULT:** 300 mg over at least 10 minutes, at induction or 15 minutes before procedure, followed by 150 mg 6 hours later by mouth or by intravenous infusion

Patient advice: Patients should discontinue treatment immediately and contact doctor if diarrhea develops; capsules should be swallowed with a glass of water.

Dilution and administration: According to manufacturer's directions

○ **Adverse effects**

- Diarrhea (discontinue treatment)

- Nausea, vomiting, abdominal discomfort, esophagitis, antibiotic-associated colitis
- Rash, pruritus, urticaria, and rarely anaphylaxis
- Erythema multiforme (Stevens-Johnson syndrome), exfoliative and vesiculobullous dermatitis
- Jaundice and altered liver function tests
- Neutropenia, eosinophilia, agranulocytosis, thrombocytopenia
- Pain, induration, and abscess after intramuscular injection
- Thrombophlebitis after intravenous injection

- **Doxycycline**

Doxycycline is a tetracycline and is a broad-spectrum antibiotic that is effective for conditions caused by chlamydia, rickettsia, Brucella, and the spirochete *Borrelia burgdorferi* (Lyme disease). It is the preferred tetracycline since it has a more favorable pharmacokinetic profile than other tetracyclines, including tetracycline. It is deposited in growing bone and teeth, causing staining and occasionally dental hypoplasia.

Doxycycline should **NOT** be given to children under 8 years or pregnant women; in some countries, use in children under 12 years is contraindicated.

- **Dosage form**

- Capsule or tablet: 100 mg (as hydrochloride)

- **Uses**

- Sinusitis
- Chronic prostatitis, syphilis, pelvic inflammatory disease
- Treatment and prophylaxis of anthrax (unlicensed indication)
- Malaria treatment and prophylaxis (Section 6.5.3)
- Recurrent aphthous ulceration, adjunct to gingival scaling and root planing for periodontitis
- Oral herpes simplex
- Rosacea, acne vulgaris
- Trachoma, psittacosis, salpingitis, urethritis, and lymphogranuloma venereum
- Rickettsia (including Q fever), Brucella (doxycycline with either streptomycin or rifampicin), and the spirochete *Borrelia burgdorferi* (Lyme disease)
- Also used in respiratory and genital mycoplasma infections, in acne, in destructive (refractory) periodontal disease, in exacerbations of chronic bronchitis (because of their activity against *Hemophilus influenzae*), and for leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin)

- **Contraindications**

- Pregnancy: Appendix B
- Children under 8 years

- Porphyria
- Systemic lupus erythematosus
- **Precautions**
 - Avoid exposure to sunlight or sunlamps (photosensitivity reported)
 - Renal impairment: Appendix D
 - Hepatic impairment: Appendix E
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A
- **Dose**

For susceptible organisms, by mouth

- **ADULT** and child over 8 years: 200 mg on first day, then 100 mg daily

Severe infections (including refractory urinary tract infections)

- 200 mg daily

Early syphilis

- 100 mg twice daily for 14 days

Late latent syphilis

- 100 mg twice daily for 28 days

Neurosyphilis

- 200 mg twice daily for 28 days

Uncomplicated genital chlamydia, non-gonococcal urethritis

- 100 mg twice daily for 7 days (14 days in pelvic inflammatory disease)

Lyme disease

- 100 mg twice daily for 10–14 days (28 days in Lyme arthritis)

Anthrax

- Treatment or post-exposure prophylaxis: 100 mg twice daily
- **CHILD** (only if alternative antibacterial cannot be given) (unlicensed dose): 5 mg/kg daily in 2 divided doses (max. 200 mg daily)

Cholera with severe dehydration only, by mouth

- **ADULT:** 300 mg as a single dose
- **CHILD** over 8 years: 100 mg as a single dose

Patient advice: Capsules (or tablets) should be swallowed whole with plenty of fluid while sitting or standing to prevent esophageal irritation. The drug may be given with food or milk to counter gastric irritation.

○ **Adverse effects**

- Gastrointestinal disturbances
- Anorexia
- Flushing, tinnitus
- Photosensitivity
- Hypersensitivity reactions (including rash, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria, angioedema, anaphylaxis, and pericarditis)
- Headache and visual disturbances

- Hepatotoxicity, blood disorders, pancreatitis and antibiotic-associated colitis reported
- Staining of growing teeth and occasional dental hypoplasia

- **Erythromycin**

Erythromycin is a macrolide; it has an antibacterial spectrum that is similar but not identical to penicillin and is used as an alternative in penicillin-allergic patients.

Erythromycin is a representative macrolide antibiotic. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 200 mg and 400 mg (ethylsuccinate); 250 mg and 500 mg (stearate)
- Oral ingestion suspension: 100 mg/5 ml (ethyl succinate) and 125 mg/5 ml (base)
- Topical solution 2% (base)

- **Uses**

- Alternative to penicillin in hypersensitive patients
- Sinusitis
- Otitis externa

- Oral infections
- Cholera
- Respiratory tract infections (including pneumonia and Legionnaires' disease)
- Syphilis
- Chancroid
- Chlamydia
- Neonatal chlamydial conjunctivitis
- Non-gonococcal urethritis
- Prostatitis
- Lymphogranuloma venereum
- Campylobacter enteritis
- Relapsing fever
- Skin infections
- Diphtheria
- Diphtheria and whooping cough prophylaxis
- Q fever in children

- **Contraindications**

- Hypersensitivity to erythromycin or other macrolides
- Porphyria

- **Precautions**

- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Predisposition to QT interval prolongation (including electrolyte disturbances and concomitant use of drugs that prolong the QT interval)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

○ **Dose**

Infections due to sensitive organisms, by mouth

- **ADULT** and **CHILD** over 8 years: 250–500 mg every 6 hours, up to 4 g daily in severe infections
- **CHILD** up to 2 years: 125 mg every 6 hours, doubled in severe infections
- **CHILD** 2–8 years: 250 mg every 6 hours, doubled in severe infections

Early syphilis, by mouth

- **ADULT:** 500 mg 4 times daily for 14 days

Late latent syphilis, by mouth

- **ADULT:** 500 mg 4 times daily for 30 days

Uncomplicated genital chlamydia, non-gonococcal urethritis,

chancroid, by mouth

- **ADULT:** 500 mg 4 times daily for 7 days (14 days in lymphogranuloma venereum)

Severe infections due to sensitive organisms, by intravenous infusion

- **ADULT** and **CHILD**: 50 mg/kg daily by continuous infusion or in divided doses every 6 hours

Patient advice: Tablets and capsules should be swallowed whole.

- **Adverse effects**

- Gastrointestinal effects including nausea, vomiting, abdominal discomfort, diarrhea, and rarely antibiotic-associated colitis
- Less frequently urticaria, rash, and other allergic reactions (rarely anaphylaxis)
- Reversible hearing loss after large doses
- Cholestatic jaundice, infantile hypertrophic pyloric stenosis, cardiac effects (including chest pain and arrhythmias), myasthenia-like syndrome, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis

- **Gentamicin**

Gentamicin is a representative aminoglycoside antibiotic. Various medicines can serve as alternatives.

- **Dosage form**

- Injection solution: 10 mg/ml, 20 mg/ml, and 40 mg/ml in 2 ml ampoules

- **Uses**

- Pneumonia
- Cholecystitis
- Peritonitis
- Septicemia
- Acute pyelonephritis
- Prostatitis
- Otitis externa
- Skin and soft tissue infections
- Pelvic inflammatory disease (with clindamycin)
- Endocarditis
- Meningitis
- Listeriosis
- Tularemia
- Brucellosis
- Plague
- Surgical prophylaxis
- Eye infections (Section 21.1)

- **Contraindications**

- Myasthenia gravis

- **Precautions**

- Renal impairment (reduce dose): Appendix D
- Neonates, infants, and the elderly (adjust dosage 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)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Dose**

Infections due to susceptible organisms, by intramuscular injection or by slow intravenous injection (over at least 3 minutes) or by intravenous infusion

- **ADULT:** 3–5 mg/kg daily in divided doses every 8 hours
- **NEONATE** up to 2 weeks: 3 mg/kg every 12 hours
- **CHILD** 2 weeks–12 years: 2 mg/kg every 8 hours

Pelvic inflammatory disease (with clindamycin), by intravenous injection

- **ADULT:** 1.5 mg/kg every 8 hours

Endocarditis (as part of combination therapy), by intramuscular injection or by intravenous injection (over at least 3 minutes)

- **ADULT:** 1 mg/kg every 8 hours

Surgical prophylaxis (with clindamycin), by intravenous injection

- **ADULT:** 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 less than 2 mg/L (less than 1 mg/L in endocarditis).

Dilution and administration: According to manufacturer’s directions

- **Adverse effects**

- Vestibular and auditory damage, nephrotoxicity
- Rarely hypomagnesaemia on prolonged therapy
- Antibiotic-associated colitis, stomatitis
- Also nausea, vomiting, rash, and blood disorders

- **Metronidazole**

Metronidazole has high activity against anaerobic bacteria and protozoa (*see also* Section 6.5.1). Metronidazole by the rectal route is an effective alternative to the intravenous route when oral administration is not possible (*suppository form not*

in LML Afghanistan). Metronidazole is a representative antibacterial and antiprotozoal drug. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 200 mg, 250 mg, 400 mg, and 500 mg
- Infusion solution: 5 mg/ml in 100 ml bottle
- Topical ointment: 0.75% in 15 g tube
- Oral ingestion suspension: 120 mg/5 ml in 100 ml bottle, 200 mg/5 ml in 60 ml bottle

- **Uses**

- Anaerobic bacterial infections, including gingivitis and other oral infections, pelvic inflammatory disease (with doxycycline and either ciprofloxacin or ceftriaxone), tetanus, septicemia, peritonitis, brain abscess, necrotizing pneumonia, antibiotic-associated colitis, leg ulcers and pressure sores, and surgical prophylaxis
- Bacterial vaginosis
- Skin and soft tissue infections, animal bites (with doxycycline)
- Tissue nematode infections, in particular, dracunculiasis (Section 6.1.1)
- Trichomonal vaginitis, amoebiasis, and giardiasis (Section 6.5.1)
- *Helicobacter pylori* eradication (Section 17.1)
- Crohn's disease (Section 17.3)

- **Contraindications**

- Chronic alcohol dependence

- **Precautions**

- Disulfiram-like reaction with alcohol
- Hepatic impairment and hepatic encephalopathy: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Clinical and laboratory monitoring recommended in courses lasting longer than 10 days
- **Interactions:** Appendix A

- **Dose**

Anaerobic infections (usually treated for 7 days), by mouth

- **ADULT:** 800 mg initially, then 400 mg every 8 hours or 500 mg every 8 hours
- **CHILD:** 7.5 mg/kg every 8 hours

Anaerobic infections, by intravenous infusion over 20 minutes

- **ADULT:** 500 mg every 8 hours
- **CHILD:** 7.5 mg/kg every 8 hours

Bacterial vaginosis, by mouth

- **ADULT:** 2 g as a single dose or 400–500 mg twice daily for 5–7 days

Pelvic inflammatory disease, by mouth

- **ADULT:** 400–500 mg twice daily for 14 days

Leg ulcers and pressure sores, by mouth

- **ADULT:** 400 mg every 8 hours for 7 days

Acute ulcerative gingivitis, by mouth

- **ADULT:** 200–250 mg every 8 hours for 3 days
- **CHILD** 1–3 years: 50 mg every 8 hours for 3 days
- **CHILD** 3–7 years: 100 mg every 12 hours for 3 days
- **CHILD** 7–10 years: 100 mg every 8 hours for 3 days

Acute oral infections, by mouth

- **ADULT:** 200 mg every 8 hours for 3–7 days
- **CHILD** 1–3 years: 50 mg every 8 hours for 3–7 days
- **CHILD** 3–7 years: 100 mg every 12 hours for 3–7 days
- **CHILD** 7–10 years: 100 mg every 8 hours for 3–7 days

Antibiotic-associated colitis, by mouth

- **ADULT:** 800 mg initially, then 400 mg 3 times daily for 10 days

Surgical prophylaxis, by mouth

- **ADULT:** 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
- **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

Surgical prophylaxis by intravenous infusion

- **ADULT:** 500 mg at induction; up to 3 further doses of 500 mg may be given every 8 hours for high-risk procedures
- **CHILD:** 7.5 mg/kg at induction; up to 3 further doses of 7.5 mg/kg may be given every 8 hours for high-risk procedures

Patient advice: Tablets should be swallowed whole with water, with or after food; suspension best taken 1 hour before food (or on an empty stomach).

- **Adverse effects**

- Nausea, vomiting, unpleasant metallic taste, “furred” tongue, and gastrointestinal disturbances
- Rarely headache, drowsiness, dizziness, ataxia, darkening of urine, erythema multiforme, pruritus, urticaria, angioedema, and anaphylaxis
- Abnormal liver function tests, hepatitis, jaundice, thrombocytopenia, aplastic anaemia, myalgia, arthralgia
- Peripheral neuropathy, epileptiform seizures, and leukopenia on prolonged or high-dosage regimens

- **Nalidixic acid**

- **Dosage form**

- Tablets: 250 mg and 500 mg
- Oral suspension: 150 mg* and 250 mg per 5 ml

- **Uses**

- Uncomplicated urinary tract infections

- **Contraindications**

- Hypersensitivity to quinolones

- **Precautions**

- History of epilepsy or conditions predispose to seizure attacks, G6PD deficiency
- Myasthenia gravis (risk of precipitation)
- Children and adolescents
- Avoid prolonged exposure to sunlight (avoid in case of photosensitivity).
- Avoid in acute porphyria.
- False-positive urinary glucose (if tested for reducing substances)
- Monitor blood count and renal and liver function if treatment exceeds 2 weeks.
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix B.
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Dose**

- **ADULT:** 900 mg every 6 hours for 7 days, reduced in chronic infections to 600 mg every 6 hours
- **CHILD** 3 months–12 years: 12.5 mg/kg 4 times daily for 7 days, reduced to 7.5 mg/kg 4 times daily in prolonged therapy or 15 mg/kg twice daily for prophylaxis
- **CHILD** 12–18 years: 900 mg 4 times daily for 7 days, reduced in chronic infections to 600 mg 4 times daily

- **Adverse effects**

- Nausea, vomiting, dyspepsia, abdominal pain, diarrhea (rarely antibiotic associated colitis)
- Headache, dizziness, weakness, sleep disturbances
- Rash (very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis)
- Less frequently anorexia, sleep disturbances, asthenia, confusion, anxiety, depression, hallucinations, tremor, blood disorders (including eosinophilia, leucopenia, thrombocytopenia), arthralgia, myalgia, disturbances in vision and taste
- Rarely or very rarely hepatic dysfunction (including jaundice and hepatitis), hypotension, vasculitis, dyspnea, convulsions, psychoses, paresthesia, renal failure, interstitial nephritis, tendon inflammation and

damage (*see also* Tendon damage above, *under* Ciprofloxacin),
photosensitivity, disturbances in hearing and smell

- The drug should be discontinued if psychiatric, neurological, or hypersensitivity reactions (including severe rash) occur.
- Also reported toxic psychosis, increased intracranial pressure, cranial nerve palsy, metabolic acidosis

- **Nitrofurantoin**

Nitrofurantoin is bactericidal in vitro to most gram-positive and gram-negative urinary tract pathogens and it is used to treat acute and recurrent urinary tract infections. It is also used prophylactically in chronic urinary tract infections.

- **Dosage form**

- Tablet: 100 mg

- **Uses**

- Urinary tract infections

- **Contraindications**

- Impaired renal function: Appendix D

- Infants younger than 3 months

- G6PD-deficiency including breast-feeding of affected infants:

Appendix C

- Pregnancy at term: Appendix B

- Porphyria

- **Precautions**

- Pulmonary disorders
- Hepatic impairment: Appendix E
- Monitor lung and liver function on long-term therapy (discontinue if lung function deteriorates)
- Neurological or allergic disorders
- Anemia
- Diabetes mellitus
- Elderly and debilitated
- Vitamin B and folate deficiency
- Use may result in false-positive urinary glucose (if testing for reducing substances).
- Urine may be colored yellow or brown.

- **Dose**

Acute uncomplicated urinary tract infections, by mouth

- **ADULT:** 100 mg every 12 hours or 50 mg every 6 hours with food for 7 days
- **CHILD** over 3 months: 3 mg/kg daily in 4 divided doses

Severe recurrent urinary tract infection, by mouth

- **ADULT:** 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, by mouth

- **ADULT:** 50–100 mg at night
- **CHILD** over 3 months: 1 mg/kg at night (with regular monitoring of lung and liver function)

○ **Adverse effects**

- Dose-related gastrointestinal disorders
- Nausea
- Hypersensitivity reactions including urticaria, rash, sialadenitis, pruritus, and angioedema
- Anaphylaxis reported
- Rarely cholestatic jaundice, hepatitis, and exfoliative dermatitis
- Erythema multiforme, pancreatitis, arthralgia
- Blood disorders
- Pulmonary reactions (including pulmonary fibrosis; possible association with lupus erythematosus-like syndrome)
- Peripheral neuropathy
- Benign intracranial hypertension
- Transient alopecia

● **Sulfamethoxazole + trimethoprim**

Also known as **co-trimoxazole**

Sulfamethoxazole is used in combination with trimethoprim because of their synergistic activity. In some countries, indications for the use of this combination have been restricted. The treatment of *Pneumocystis carinii* (*Pneumocystis jiroveci*) infections must only be undertaken with specialist supervision where there are appropriate monitoring facilities.

- **Dosage form**

- Tablets: Sulfamethoxazole + trimethoprim 100 mg + 20 mg, 400 mg + 80 mg, 800 mg + 160 mg
- Oral suspension: 200 mg + 40 mg/5 ml, 400 mg + 80 mg/5 ml

- **Uses**

- Urinary tract infections
- Respiratory tract infections including bronchitis, pneumonia, and infections in cystic fibrosis
- Typhoid fever
- Melioidosis
- Listeriosis
- Brucellosis
- Granuloma inguinale
- Neonatal chlamydial conjunctivitis
- Otitis media
- Skin infections, animal bites
- *Pneumocystis carinii* (*Pneumocystis jiroveci*) pneumonia (Section 6.5.4)

- **Contraindications**

- Hypersensitivity to sulfonamides or trimethoprim
- Porphyria

- **Precautions**

- Renal impairment (avoid if severe): Appendix D
- Hepatic impairment (avoid if severe): Appendix E
- Maintain adequate fluid intake (to avoid crystalluria)
- Blood disorders (avoid unless under specialist supervision; monitor blood counts and discontinue immediately if blood disorder develops)
- Rash (discontinue immediately)
- Predisposition to folate deficiency or hyperkalemia

- Elderly
- Asthma
- G6PD deficiency
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Avoid in infants under 6 weeks
- **Interactions:** Appendix A

○ **Dose**

Infections due to susceptible organisms (that are not susceptible to other antibacterials), by mouth

- **ADULT:** Sulfamethoxazole 800 mg + trimethoprim 160 mg every 12 hours, increased to sulfamethoxazole 1.2 g + trimethoprim 240 mg every 12 hours in more severe infections
- **CHILD** 6 weeks–5 months: Sulfamethoxazole 100 mg + trimethoprim 20 mg every 12 hours
- **CHILD** 6 months–5 years: Sulfamethoxazole 200 mg + trimethoprim 40 mg every 12 hours
- **CHILD** 6–12 years: Sulfamethoxazole 400 mg + trimethoprim 80 mg every 12 hours

By intravenous infusion

- **ADULT:** Sulfamethoxazole 800 mg + trimethoprim 160 mg every 12 hours, increased to sulfamethoxazole 1.2 g + trimethoprim 240 mg, every 12 hours in more severe infections
- **CHILD:** Sulfamethoxazole 30 mg/kg daily + trimethoprim 6 mg/kg daily in 2 divided doses

Dilution and administration: According to manufacturer's directions

- **Adverse effects**
 - Nausea, diarrhea
 - Headache
 - Hyperkalemia
 - Hypersensitivity reactions including rash and very rarely, Stevens-Johnson syndrome, toxic epidermal necrolysis, and photosensitivity (discontinue immediately)
 - Less commonly vomiting
 - Very rarely glossitis, stomatitis, anorexia, liver damage (including jaundice and hepatic necrosis), pancreatitis, antibiotic-associated colitis, myocarditis, cough and shortness of breath, pulmonary infiltrates, aseptic meningitis, depression, convulsions, peripheral neuropathy, ataxia, tinnitus, vertigo, hallucinations, hypoglycemia, blood disorders (including leukopenia, thrombocytopenia, megaloblastic anemia, and eosinophilia), hyponatremia, renal disorders (including interstitial nephritis), arthralgia, myalgia, vasculitis, and systemic lupus erythematosus

6.2.3 Antileprosy medicines

Leprosy is a chronic mycobacterial infection due to *Mycobacterium leprae*, which is a slow-growing intracellular bacillus that infiltrates the skin, peripheral nerves, the nasal and other mucosa, and the eyes; it affects people of all ages and both sexes. The incubation period between infection and appearance of leprosy is normally between 2 and 10 years, but may be up to 20 years. It is transmitted from person-to-person when bacilli are shed from the nose; most individuals have natural immunity and symptoms are suppressed. For treatment purposes, patients may be classified as having either paucibacillary (PB) or multibacillary (MB) leprosy. The two forms may be distinguished by skin smears, but facilities are not always available to process them and their reliability is often doubtful. In practice, most leprosy programs classify and choose a regimen based on the number of skin lesions; these are PB leprosy, 1–5 skin lesions, and MB leprosy, more than 5 skin lesions.

Medicines for the treatment of leprosy should always be used in combination; this is essential to prevent the emergence of resistance. **Rifampicin** is now combined with **dapsone** to treat PB leprosy, and rifampicin and **clofazimine** are now combined with **dapsone** to treat MB leprosy. The WHO Programme for the Elimination of Leprosy currently provides, free of charge, oral multidrug therapy (MDT) in color-coded blister packs (MDT blister packs) to improve patients' adherence to treatment. Any patient with a positive skin smear should be treated with the MDT regimen for MB leprosy. The regimen for PB leprosy should never be given to a patient with MB leprosy. If diagnosis classification in a particular patient is not possible, then the MDT regimen for MB leprosy must be used.

Lepra reactions are episodes of sudden increase in the activity of leprosy and are often accompanied by neuritis; reactions must always be treated promptly to prevent permanent nerve damage and disability. Leprosy MDT should continue during a lepra reaction without interruption. This reduces the frequency and severity of lepra reactions.

Type 1 lepra reactions, or reversal reactions, are delayed hypersensitivity reactions and may occur in either PB or MB leprosy. If there is no nerve damage, type 1 reactions may be treated with analgesics such as acetylsalicylic acid or paracetamol (Section 2.1). If there is nerve involvement, corticosteroids such as oral prednisolone (Section 3) should be used in addition to analgesics.

The type 2 lepra reaction, also known as erythema nodosum leprosum (ENL), is an antibody response to dead leprosy bacteria and occurs in MB leprosy only. Therapy for type 2 reactions may include analgesics, such as acetylsalicylic acid or paracetamol, and a corticosteroid, such as oral prednisolone. In patients not responding to a corticosteroid, clofazimine may be used. Severe type 2 lepra reactions should be treated under medical supervision in the hospital.

If a patient does not respond to lepra reaction treatment within 6 weeks or their condition worsens, the patient must be sent immediately to the nearest specialist center. Neuritis

may occur during, or independently of, lepra reactions. It can be successfully treated with a 12-week course of oral prednisolone (Section 18.1); if patients do not respond, specialist center treatment is required.

Treatment regimens

The recommended regimen for PB leprosy in adults (50–70 kg) is rifampicin, 600 mg once monthly, and dapsone, 100 mg daily. **CHILDREN** aged 10–14 years may be given rifampicin, 450 mg once monthly, and dapsone, 50 mg daily. Appropriate dose adjustments are required for younger children. For example, dapsone, 25 mg daily, and rifampicin, 300 mg once a month. In PB leprosy, treatment is continued for 6 months.

The recommended regimen for MB leprosy in **ADULTS** (50–70 kg) is rifampicin, 600 mg, and clofazimine, 300 mg, both given once a month together with clofazimine, 50 mg, and dapsone, 100 mg, both daily. **CHILDREN** aged 10–14 years may be given rifampicin, 450 mg, and clofazimine, 150 mg, both once a month together with clofazimine, 50 mg every other day, and dapsone, 50 mg daily. Appropriate dosage adjustments are required for younger children. For example, dapsone, 25 mg daily, clofazimine, 50 mg twice a week, and clofazimine, 100 mg, and rifampicin, 300 mg once a month. In MB leprosy, treatment is continued for 12 months.

For patients who cannot take rifampicin because of allergy, other diseases, or rifampicin-resistant leprosy, and for patients who refuse to take clofazimine, there are alternative regimens, which incorporate ofloxacin and minocycline.

- **Clofazimine**

- **Dosage from**

- Capsules: 50 mg and 100 mg

- **Uses**

- Multibacillary leprosy; type 2 lepra reactions

- **Precautions**

- Preexisting gastrointestinal symptoms (reduce dose; increase dose interval or discontinue if symptoms develop during treatment)
- Liver and renal impairment
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- May discolor soft contact lenses

- **Dose**

Multibacillary leprosy (in combination with dapsone and rifampicin; see also introductory note above), by mouth

- **ADULT:** 50 mg once daily and 300 mg once a month
- **CHILD** 10–14 years: 50 mg on alternate days and 150 mg once a month
- **CHILD** under 10 years: see introductory note above; continue treatment for 12 months

Type 2 lepra reaction (erythema nodosum leprosum), by mouth

- **ADULT** and **CHILD:** 200–300 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

- **Adverse effects**

- Reversible discoloration of skin, hair, cornea, conjunctiva, tears, sweat, sputum, feces, and urine
- Dose-related gastrointestinal symptoms including pain, nausea, vomiting, diarrhea, weight loss, and gastrointestinal bleeding
- Severe mucosal and sub-mucosal edema, with prolonged treatment with high doses (may be severe enough to cause sub-acute small-bowel obstruction; see also Precautions)
- Dry skin, acne-like eruptions, rash, pruritus, photosensitivity reactions, decreased sweat production

- Dry eyes
- Rarely headache, drowsiness, dizziness, taste disorders, and elevation of blood glucose concentration

- **Dapsone**

- **Dosage form**

- Tablets: 25 mg, 50 mg, and 100 mg

- **Uses**

- Paucibacillary and multibacillary leprosy

- **Contraindications**

- Hypersensitivity to sulfones
- Severe anemia

- **Precautions**

- Anemia (treat severe anemia before commencement of therapy and monitor blood count during treatment)
- Susceptibility to hemolysis including G6PD deficiency (including breast-feeding affected infants)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Porphyria
- **Interactions:** Appendix A

Blood disorders: On long-term treatment, patients and their carers 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.

- **Dose**

Paucibacillary leprosy (in combination with rifampicin), by mouth

- **ADULT:** 100 mg daily
- **CHILD** under 10 years: *See* introductory note above
- **CHILD** 10–14 years: 50 mg daily, *see* introductory note above; continue treatment for 6 months

Multibacillary leprosy (in combination with rifampicin and clofazimine, see introductory note above)

- **ADULT:** 100 mg daily
- **CHILD** under 10 years: *See also* introductory note above
- **CHILD** 10–14 years: 50 mg daily, *see* introductory note above; continue treatment for 12 months

- **Adverse effects**

- Hemolysis and methemoglobinemia
- Allergic dermatitis (rarely including toxic epidermal necrolysis and Stevens-Johnson syndrome)
- Rarely hepatitis and agranulocytosis
- “Dapsone syndrome,” resembling mononucleosis (a rare hypersensitivity reaction with symptoms including rash, fever, jaundice, and eosinophilia)
- Gastrointestinal irritation
- Tachycardia, headache, nervousness, insomnia, blurred vision, paresthesia, reversible peripheral neuropathy, and psychoses reported

- **Rifampicin**

- **Dosage form**

- Capsules or tablets: 150 mg and 300 mg

- **Uses**

- Paucibacillary leprosy
- Multibacillary leprosy
- Meningitis
- Tuberculosis (Section 6.2.4)
- **Contraindications**
 - Hypersensitivity to rifampicin
 - Jaundice
- **Precautions**
 - Hepatic impairment (reduce dose): Appendix E
 - Monitor liver function and blood counts in liver disorders, alcohol dependency, elderly, and in those on prolonged therapy
 - Renal impairment (if dose above 600 mg daily): Appendix D
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Porphyria
 - Discolors soft contact lenses
 - **Important:** Advise patients on oral contraceptives to use additional means.
 - **Interactions:** Appendix A

Note: Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, hemolysis, or thrombocytopenia; discontinue permanently if serious adverse effects occur.

Liver disorders: Patients or their carers 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.

- **Dose**

Paucibacillary leprosy (in combination with dapsone; see also introductory note above), by mouth

- **ADULT:** 600 mg once a month
- **CHILD** 10–14 years: 450 mg once a month
- **CHILD** under 10 years: see introductory note above; continue treatment for 6 months

Multibacillary leprosy (in combination with dapsone and clofazimine; see note above), by mouth

- **ADULT:** 600 mg once a month under supervision
- **CHILD** under 10 years: see note above
- **CHILD** 10–14 years: 450 mg once a month under supervision; continue treatment for 12 months

Patient advice: Take dose at least 30 minutes before a meal, since absorption is reduced by food.

○ **Adverse effects**

- Severe gastrointestinal disturbances including anorexia, nausea, vomiting, and diarrhea (antibiotic-associated colitis reported)
- Headache, drowsiness
- Rash, fever, influenza-like syndrome and respiratory symptoms, collapse, shock, hemolytic anemia, acute renal failure, and thrombocytopenic purpura (more frequent with intermittent therapy)
- Alterations of liver function: jaundice, and potentially fatal hepatitis (dose-related; do not exceed max. daily dose of 600 mg)
- Edema, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia, and menstrual disturbances also reported
- Urine, tears, saliva, and sputum colored orange-red

6.2.4 Antituberculosis medicines

Also refer to the protocols of the National Tuberculosis Program of Afghanistan.

Tuberculosis is a chronic infectious disease caused primarily by *Mycobacterium tuberculosis*, or sometimes *M. bovis*. Infection is usually due to inhalation of infected droplet nuclei, with the lung generally being the first organ affected. The primary infection is usually asymptomatic, and infection and inflammatory responses resolve with the development of acquired immunity. Surviving bacteria may become dormant, or in susceptible patients, may progress to active primary disease; dormant organisms may later produce disease and this often occurs if immune status is altered.

Tuberculosis is the most prevalent infectious disease of adults and causes 26% of avoidable adult deaths in the developing world. More than 80% of tuberculosis cases are pulmonary (PTB). At least 30% of patients who are infected with HIV will also develop active tuberculosis.

The increase in resistant strains and poor compliance has led to the development of new, simplified drug regimens for the treatment of TB. Directly observed treatment, short-course (DOTS), which lasts for 6 or 8 months and is administered under direct observation, is one of the most important components of the WHO strategy against tuberculosis. Simplified drug regimens and intermittent therapy have been introduced to improve compliance. WHO does not generally recommend twice-weekly regimens. If a patient receiving a twice-weekly regimen misses a dose of tablets, the missed dose represents a bigger fraction of the total number of treatment doses than if the patient were receiving a 3-times weekly or daily-dose regimen. Therefore, a greater risk of treatment failure exists with twice-weekly regimens. Fixed-dose combination tablets incorporating two or more drugs are used to improve compliance and decrease medication errors; they should be used unless one of the components cannot be given because of resistance or intolerance.

The modern short-course therapy is usually in 2 phases. The initial phase (2 months) involves the concurrent use of at least 3 drugs to reduce the bacterial population rapidly

and prevent drug-resistant bacteria from emerging. The second (continuation) phase (4–6 months) involves fewer drugs and is intended to eliminate any remaining bacteria and prevent recurrence. Direct observation of therapy is considered essential to ensure compliance in the initial phase and is also useful in the continuation phase, especially if patients are receiving rifampicin. Five antituberculosis drugs, **isoniazid, rifampicin, pyrazinamide, streptomycin** (which are bactericidal), and **ethambutol** (which is bacteriostatic), are used in various combinations as part of WHO-recommended treatment regimens. In supervised regimens, a change of drug regimen should be considered only if the patient fails to respond after 5 months of DOTS. Isoniazid, rifampicin, and pyrazinamide are components of all antituberculosis drug regimens currently recommended by WHO. Unsupervised and alternative regimens as set out in tables 6.1 and 6.2 may be administered as specified.

Additional reserve antituberculosis drugs (**amikacin, p-aminosalicylic acid, capreomycin, cycloserine, ethionamide, kanamycin, ofloxacin, or levofloxacin**) for the treatment of multidrug-resistant (MDR) tuberculosis should be used in specialized centers adhering to WHO standards for TB control (see table 6.3 below).

Prophylaxis

Worldwide, an important predisposing cause of immunosuppression leading to tuberculosis is HIV infection; it increases susceptibility to primary infection and increases the reactivation rate of tuberculosis. Preventive antituberculosis therapy of HIV-positive persons with isoniazid is recommended in *Tuberculosis and HIV Policy, Strategy and Practical Guidelines*, MoPH Afghanistan, 2007.

Chemoprophylaxis with **isoniazid** can prevent the development of clinically apparent disease in persons in close contact with infectious TB patients, and also prevent the reactivation of previously dormant disease in other persons at high risk, particularly those who are immunodeficient.

Where the disease remains highly prevalent, routine immunization of infants within the first year of age with bacillus Calmette–Guérin (BCG) vaccine is a cost-effective prophylactic measure. However, there is no evidence that BCG will protect children older than 15 years of age. Infants born to HIV-positive mothers should be vaccinated during the first year of life, provided they have no clinical signs suggestive of HIV.

Diagnosis

The tuberculin test has limited diagnostic value. A positive tuberculin test indicates previous exposure to mycobacterial antigens through infection with one of the tubercle bacilli or through BCG vaccination. The tuberculin test does not distinguish between tuberculosis and other mycobacterial infection, between active and quiescent disease, or between acquired infection and seroconversion induced by BCG vaccination.

Category I: New pulmonary disease (smear-positive or smear-negative with extensive involvement of parenchyma), concomitant severe HIV disease, and new severe extra-pulmonary disease

*Initial phase*¹ (antibacterials administered daily or 3 times weekly²):

Isoniazid + rifampicin + pyrazinamide + ethambutol (or streptomycin) for 2 months

*Continuation phase*¹ (antibacterials administered daily or 3 times weekly):

Isoniazid + rifampicin for 4 months (or isoniazid + ethambutol for 6 months *but less effective than* isoniazid + rifampicin)

Category II: Previously treated smear-positive pulmonary disease that has relapsed or failed³ to respond, or if treatment was interrupted

*Initial phase*¹ (antibacterials administered daily or 3 times weekly; see tables 6.1 and 6.2):

Isoniazid + rifampicin + pyrazinamide + ethambutol + streptomycin for 2 months

Then:

Isoniazid + rifampicin + pyrazinamide + ethambutol for 1 month

*Continuation phase*¹ (antibacterials administered daily or 3 times weekly; see tables 6.1 and 6.2):

Isoniazid + rifampicin + ethambutol for 5 months

Category III: New smear-negative pulmonary disease (other than in Category I) and less severe extrapulmonary disease

*Initial phase*¹ (antibacterials administered daily or 3 times weekly²):

Isoniazid + rifampicin + pyrazinamide + ethambutol⁴ for 2 months

*Continuation phase*¹ (antibacterials administered daily or 3 times weekly, based on tables 6.1 and 6.2):

Isoniazid + rifampicin for 4 months (or isoniazid + ethambutol for 6 months *but less effective than* isoniazid + rifampicin)

Category IV: Chronic and MDR-TB (smear-positive despite supervised re-treatment)

Specially designed standardized or individualized regimens are recommended.

¹ Intake of medicine in patients remaining smear-positive in initial stage. If rifampicin is prescribed, the patient should always be under direct observation.

² In the case of treatment failure, before prescribing category II, susceptibility testing should be performed; in patients with MDR-TB category IV should be applied.

³ Ethambutol in the initial phase should be withdrawn:

- If not concomitant with HIV
- In patients with fully sensitive TB bacilli
- In young children affected with TB

⁴ On-time culture and antibiotic susceptibility testing should be done in patients who have had contact with MDR-TB patients.

Table 6.1. Recommended 6-month treatment regimens for tuberculosis¹

Medicine	Initial phase (2 months)	Continuation phase (4 months)
Isoniazid	5 mg/kg daily	5 mg/kg daily
+		
Rifampicin	10 mg/kg daily	10 mg/kg daily
+		
Pyrazinamide	25 mg/kg daily	
together with		
Streptomycin ²	15 mg/kg daily	
or		
Ethambutol ³	15 mg/kg daily	
Isoniazid	10 mg/kg 3 times weekly	10 mg/kg 3 times weekly
+		
Rifampicin	10 mg/kg 3 times weekly	10 mg/kg 3 times weekly
+		
Pyrazinamide	35 mg/kg 3 times weekly	
together with		
Streptomycin ²	15 mg/kg 3 times weekly	
or		
Ethambutol	30 mg/kg 3 times weekly	

¹Unless otherwise indicated, doses are suitable for both adults and children.

²Streptomycin always replaces ethambutol in meningeal TB.

³Ethambutol 20 mg/kg is recommended in children.

Table 6.2. Recommended 8-month treatment regimen for tuberculosis¹

Medicine	Initial phase (2 months)	Continuation phase (6 months)
Isoniazid	5 mg/kg daily	5 mg/kg daily
+		
Rifampicin	10 mg/kg daily	
+		
Pyrazinamide	25 mg/kg daily	
together with		
Ethambutol	15 mg/kg daily ³	15 mg/kg daily
or		
Streptomycin ²	15 mg/kg daily	
¹ Unless otherwise indicated, doses are suitable for both adults and children.		
² Streptomycin always replaces ethambutol in meningeal TB.		
³ Ethambutol 20 mg/kg is recommended in children.		

Table 6.3. Treatment of MDR-TB

Medicine	Dosage
Amikacin (AMK)	15 mg/kg/day (6 day/week, maximum 1 g/day)
Cycloserine (CS)	750–1,000 mg/day
Ethionamide (ETH)	750–1,000 mg/day
Para-amino salicylic acid (PAS)	150 mg/kg/day (8–12 g/day)
Capreomycin (CM)	15 mg/kg/day (6 day/week, maximum 1 g/day)
Moxifloxacin (MOX)	7.5–10 mg/kg/day or 400 mg/day

- **Amikacin**

Amikacin is a complementary list medicine for the treatment of MDR-TB, which should be used in specialized centers adhering to WHO standards for tuberculosis control. (For further information on the treatment of MDR-TB, refer to the National Tuberculosis Program of Afghanistan.)

- **Dosage form**

- Injection: 50 mg/ml, 125 mg/ml, 250 mg/ml, and 500 mg/ml in 2 ml vial

- **Capreomycin**

Capreomycin is a complementary list medicine for the treatment of MDR-TB, which should be used in specialized centers adhering to WHO standards for tuberculosis control. (For further information on the treatment of MDR-TB, refer to the *National Guidelines for the Tuberculosis Program in Afghanistan*, MoPH Afghanistan, 2010.)

- **Dosage form**

- Injection: 1,000 mg in vial

- **Cycloserine**

Cycloserine is a complementary list medicine for the treatment of MDR-TB, which should be used in specialized centers adhering to WHO standards for tuberculosis control. (For further information for the treatment of MDR-TB, refer to the *National Guidelines for the Tuberculosis Program in Afghanistan*, MoPH Afghanistan, 2010.)

- **Dosage form**

- Capsule: 250 mg

- **Ethambutol**

- **Dosage form**

- Tablets: 100 mg and 400 mg (as hydrochloride)

- **Uses**

- Tuberculosis, in combination with other drugs

- **Contraindications**

- Optic neuritis
 - Children under 5 years (unable to report symptomatic visual disturbances)
 - Severe renal impairment

- **Precautions**

- Ocular examination recommended before and during treatment (*see also* Note below)
 - Renal impairment (reduce dose and monitor plasma ethambutol concentration if creatinine clearance is less than 30 ml/min): Appendix D

- Elderly
- Pregnancy: Appendix B
- Breast-feeding: Appendix C

Note: Patients should report visual disturbances immediately and discontinue treatment; children who are incapable of reporting symptomatic visual changes accurately should be given alternative therapy, as should, if possible, any patient who cannot understand warnings about visual adverse effects.

○ **Dose**

Tuberculosis (as part of a 6- or 8-month regimen; see introductory note and tables 6.1, 6.2, above), by mouth

- **ADULT:** 15 mg/kg daily or 30 mg/kg 3 times weekly
- **CHILD:** 20 mg/kg daily or 30 mg/kg 3 times a week

Note: Peak plasma concentration (measured 2–2.5 hours after dose) should be in the range 2–6 mg/L (7–22 micromole/L); trough (pre-dose) concentration should be less than 1 mg/L (4 micromole/L).

○ **Adverse effects**

- Optic neuritis, including reduced visual acuity and red/green color blindness (early changes usually reversible; prompt withdrawal may prevent blindness)
- Peripheral neuritis (especially in legs)
- Gout
- Rarely rash, pruritus, urticaria, and thrombocytopenia

• **Ethambutol + isoniazid**

○ **Dosage form**

- Tablets: 400 mg + 150 mg and 400 mg + 75 mg

- **Uses**

- Tuberculosis, in combination with other drugs

- **Contraindications**

- Combined preparation not suitable for use in children; *see also under* Ethambutol; Isoniazid

- **Precautions**

- *See under* Ethambutol; Isoniazid

- **Dose**

Tuberculosis (as part of an 8-month regimen; see introductory note and tables 6.1 and 6.2 above), by mouth

- **ADULT:** Ethambutol, 800 mg, and isoniazid, 300 mg daily

- **Adverse effects**

- *See under* Ethambutol; Isoniazid

- **Ethionamide**

Ethionamide is a complementary list medicine for the treatment of MDR-TB, which should be used in specialized centers adhering to WHO standards for tuberculosis control. (For further information on the treatment of MDR-TB, refer to the National Tuberculosis Programs of Afghanistan.)

- **Dosage form**

- Tablet: 250 mg

- **Isoniazid**

- **Dosage form**

- Tablets: 50 mg, 100 mg, and 300 mg

- **Uses**

- Tuberculosis treatment, in combination with other drugs (*see notes and tables 6.1 and 6.2 above*)
 - Tuberculosis prophylaxis

- **Contraindications**

- Drug-induced hepatic disease

- **Precautions**

- Hepatic impairment (monitor hepatic function): Appendix E
 - Malnutrition, chronic alcohol dependence, and chronic renal failure: Appendix D
 - Diabetes mellitus, HIV infection (prophylactic pyridoxine, 10 mg daily, required because of the increased risk of peripheral neuritis)
 - Epilepsy
 - Slow acetylator status (increased risk of adverse effects)
 - History of psychosis
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Porphyria
 - **Interactions:** Appendix A

Liver disorders: Patients or their carers should be told how to recognize signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as nausea, vomiting, malaise, or jaundice develop.

- **Dose**

Tuberculosis, treatment (as part of a 6- or 8-month regimen; see introductory note and tables 6.1, 6.2, and 6.3 above) by mouth

- **ADULT** and **CHILD**: 5 mg/kg (4–6 mg/kg) daily (max. 300 mg daily), or 10 mg/kg 3 times weekly

Tuberculosis, prophylaxis, by mouth

- **ADULT**: 300 mg daily for at least 6 months
- **CHILD**: 5 mg/kg daily (max. 300 mg daily) for at least 6 months

Patient advice: Isoniazid should be taken on an empty stomach; if taken with food to reduce gastrointestinal irritation, oral absorption and bioavailability may be impaired.

- **Adverse effects**

- Gastrointestinal disorders including nausea and vomiting, diarrhea and pain, constipation, and dry mouth
- Hypersensitivity reactions including fever, rash, joint pain, erythema multiforme, and purpura (usually during the first weeks of treatment)
- Peripheral neuropathy
- Blood disorders including agranulocytosis, hemolytic anemia, and aplastic anemia
- Optic neuritis, toxic psychoses, and convulsions
- Hepatitis (especially in those over age 35 years and in regular users of alcohol; withdraw treatment)
- Systemic lupus erythematosus–like syndrome, pellagra, hyperreflexia, difficulty with micturition, hyperglycemia, and gynecomastia also reported

- **Moxifloxacin**

Moxifloxacin is a complementary list medicine for the treatment of MDR-TB, which should be used in specialized centers adhering to WHO standards for tuberculosis control. (For further information for the treatment of MDR-TB, refer to the National Tuberculosis Program of Afghanistan.)

- **Dosage form**

- Tablet: 400 mg

- **Para-aminosalicylic acid**

p-aminosalicylic acid is a complementary list medicine for the treatment of MDR-TB, which should be used in specialized centers adhering to WHO standards for tuberculosis control. (For further information for the treatment of MDR-TB, refer to the *National Guidelines for the Tuberculosis Program in Afghanistan*, MoPH Afghanistan, 2010.)

- **Dosage form**

- Granules: 4 g in sachet

- **Pyrazinamide**

- **Dosage form**

- Tablets: 150 mg, 400 mg, and 500 mg

- **Uses**

- Tuberculosis, in combination with other drugs (*see* notes and tables 6.1, 6.2, and 6.3 above)

- **Contraindications**

- Severe hepatic impairment
 - Porphyria

- **Precautions**

- Hepatic impairment (monitor hepatic function): Appendix E
- Renal impairment: Appendix D
- Diabetes mellitus (monitor blood glucose—may change suddenly)
- Gout
- Pregnancy: Appendix B
- Breast-feeding: Appendix C

Liver disorders: Patients or their carers should be told how to recognize signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise, or jaundice develop.

- **Dose**

Tuberculosis (as part of a 6- or 8-month regimen; see introductory note and tables 6.1, 6.2, and 6.3 above), by mouth

- **ADULT** and **CHILD:** 25 mg/kg daily or 35 mg/kg 3 times weekly

- **Adverse effects**

- Hepatotoxicity including fever, anorexia, hepatomegaly, splenomegaly, jaundice, and liver failure
- Nausea, vomiting
- Flushing
- Dysuria
- Arthralgia
- Gout
- Sideroblastic anemia
- Rash, photosensitivity

- **Rifampicin + isoniazid + ethambutol**

- **Dosage form**

- Tablet: 150 mg + 75 mg + 275 mg

- **Uses**

- Tuberculosis, in combination with other drugs

- **Contraindications**

- *See under* Isoniazid; Ethambutol; Rifampicin

- **Precautions**

- Combined preparation usually not suitable for use in children; *see also under* Isoniazid; Ethambutol; Rifampicin

- **Dose**

Tuberculosis (as part of an 8-month regimen; see introductory note and table 6.2 above), by mouth

- **ADULT:** Rifampicin, 10 mg/kg, isoniazid, 5 mg/kg, and ethambutol 15 mg/kg daily; *or* rifampicin, 10 mg/kg, isoniazid, 10 mg/kg, and ethambutol, 30 mg/kg, 3 times a week
- **CHILD:** Rifampicin, 10 mg/kg, isoniazid, 5 mg/kg, and ethambutol, 20 mg/kg daily; *alternatively* rifampicin, 10 mg/kg, isoniazid, 10 mg/kg, and ethambutol, 30 mg/kg 3 times a week

- **Adverse effects**

- *See under* Isoniazid; Ethambutol; Rifampicin

- **Rifampicin + isoniazid**

- **Dosage form**

- Tablets: 60 mg + 30 mg and 150 mg + 75 mg

- **Uses**

- Tuberculosis, in combination with other drugs (*see notes and tables 6.1, 6.2, and 6.3 above*)

- **Contraindications**

- *See under* Isoniazid; Rifampicin

- **Precautions**

- Combined preparation usually not suitable for use in children
- *See also under* Isoniazid; Rifampicin

- **Dose**

Tuberculosis (as part of a 6-month regimen; see introductory note and table 6.1, above), by mouth

- **ADULT:** Rifampicin, 10 mg/kg, and isoniazid, 5 mg/kg, daily

Tuberculosis (as part of a 6-month regimen; see introductory note and tables 6.1above), by mouth

- **ADULT:** Rifampicin, 10 mg/kg, and isoniazid, 10 mg/kg, 3 times weekly

- **Adverse effects**

- *See under* Isoniazid; Rifampicin

- **Rifampicin + isoniazid + pyrazinamide**

- **Dosage form**

- Tablet: 60 mg + 30 mg + 150 mg (for intermittent use, 3 times weekly)

- **Uses**

- Tuberculosis, in combination with other drugs

- **Contraindications**

- Combined preparation not suitable for use in children
 - *See also under* Isoniazid; Pyrazinamide; Rifampicin

- **Precautions**

- *See under* Isoniazid; Pyrazinamide; Rifampicin

- **Dose**

Tuberculosis (as part of a 6-month regimen; see introductory note and table 6.1 above), by mouth

- **ADULT:** Rifampicin, 10 mg/kg, isoniazid, 5 mg/kg, and pyrazinamide, 25 mg/kg, daily; *or* rifampicin, 10 mg/kg, isoniazid, 10 mg/kg, and pyrazinamide, 35 mg/kg, 3 times weekly

- **Adverse effects**

- *See under* Isoniazid; Pyrazinamide; Rifampicin

- **Rifampicin + isoniazid + pyrazinamide + ethambutol**

- **Dosage form**

- Tablet: 150 mg + 75 mg + 400 mg + 275 mg

- **Uses**

- Tuberculosis, alone or in combination with other drugs

- **Contraindications**

- Combined preparation not suitable for use in children
- *See also under* Ethambutol; Isoniazid; Pyrazinamide; Rifampicin

- **Precautions**

- *See under* Ethambutol; Isoniazid; Pyrazinamide; Rifampicin

- **Dose**

Tuberculosis (as part of a 6-month regimen; see introductory note and tables 6.1, 6.2, and 6.3 above), by mouth

- **ADULT:** Rifampicin, 10 mg/kg, isoniazid, 5 mg/kg, pyrazinamide, 25 mg/kg, and ethambutol, 15 mg/kg, daily

- **Adverse effects**

- *See under* Ethambutol; Isoniazid; Pyrazinamide; Rifampicin

- **Streptomycin**

- **Dosage form**

- Injection: 1 g (as sulfate) in vial

- **Uses**

- Tuberculosis, in combination with other drugs
- Tularemia
- Plague
- Brucellosis (with doxycycline; Section 6.2.2)

- **Contraindications**

- Hearing disorders

- Myasthenia gravis
- Pregnancy: Appendix B
- **Precautions**
 - Children (painful injection, avoid use if possible)
 - Renal impairment: Appendix D
 - Infants and the elderly (adjust dose and monitor renal, auditory, and vestibular function, and plasma streptomycin concentrations)
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A
- **Dose**

Tuberculosis (as part of a 6- or 8-month regimen; see introductory note and tables 6.1, 6.2, and 6.3 above), by deep intramuscular injection

 - **ADULT** and **CHILD:** 15 mg/kg daily or 3 times weekly (patients over 60 years or those weighing less than 50 kg may not tolerate doses above 500–750 mg daily)

Reconstitution and administration: According to manufacturer's directions

Note: 1-hour (peak) plasma concentration should be 15–40 mg/L; pre-dose (trough) concentration should be less than 5 mg/L (less than 1 mg/L in renal impairment or those over 50 years).
- **Adverse effects**
 - Vestibular and auditory damage, nephrotoxicity
 - Hypersensitivity reactions (withdraw treatment)
 - Paresthesia of mouth
 - Rarely hypomagnesaemia on prolonged therapy
 - Antibiotic-associated colitis

- Also nausea, vomiting, and rash
- Rarely hemolytic anemia, aplastic anemia, agranulocytosis, and thrombocytopenia
- Pain and abscess at injection site

6.3 ANTIFUNGAL MEDICINES

Fungal infections can be superficial or systemic. Superficial infections affect only the skin, hair, nails, or mucous membranes, whereas systemic fungal infections affect the body as a whole.

Systemic fungal infections are sometimes caused by inhalation, ingestion, or inoculation of primary pathogens, and sometimes by opportunistic invasion of commensals in patients with lowered host resistance. They are increasing in prevalence not only because of the pandemic of HIV infection, but also because of the rise in illicit intravenous drug use in many countries, as well as greater use of broad-spectrum antibiotics and invasive medical procedures. In immunodeficient patients, systemic fungal infections are often disseminated.

Amphotericin B is a lipophilic polyene antibiotic; it is fungistatic against a broad spectrum of pathogenic fungi, including *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Mucor*, *Absidia*, and *Phicopes* spp.; it is also active against algal *Prototheca* spp. and the *Leishmania* protozoa. It is used for the empirical treatment of serious fungal infections and is used alone or in conjunction with **flucytosine** to treat cryptococcal meningitis and systemic candidiasis.

Amphotericin B has to be administered parenterally as there is little or no absorption from the gastrointestinal tract; amphotericin B can be nephrotoxic. Duration of therapy depends on the initial severity of the infection and the clinical response of the patient. In some infections, a satisfactory response is obtained only after several months of

continuous treatment. Lipid formulations of amphotericin B for intravenous infusion are significantly less toxic, but are much more expensive.

Clotrimazole is an imidazole antifungal that is effective in short courses for the treatment of vaginal candidiasis. Treatment involves insertion of pessaries (vaginal tablets) or cream high into the vagina (including during menstruation). Recurrent infection may be treated with a high-dose pessary every week for 6 months.

Fluconazole, an orally active synthetic imidazole derivative, possesses fungistatic activity against dermatophytes, yeasts, and other pathogenic fungi. It is widely used in the treatment of serious gastrointestinal and systemic mycoses, such as ringworm, as well as in the management of superficial infections. Fluconazole is also used to prevent fungal infections in immunocompromised patients.

Flucytosine (*not in LML Afghanistan*) is a synthetic fluorinated pyrimidine with a narrow spectrum of antifungal activity, but which is particularly effective against *Cryptococcus* and *Candida* spp. In susceptible fungi, it is converted to fluorouracil by cytosine deaminase. Flucytosine is myelosuppressive and plasma concentrations above 75 micrograms/mL are associated with myelotoxicity.

Griseofulvin is a fungistatic antibiotic derived from *Penicillium griseofulvum* with selective activity against the dermatophytes causing ringworm, *Microsporum canis*, *Trichophyton rubrum*, and *T. verrucosum*. It has no activity against pityriasis versicolor or candida infections. Griseofulvin is deposited selectively in keratin precursor cells of skin, hair, and nails, where it disrupts the mitotic apparatus of fungal cells, thus preventing fungal invasion of newly formed cells. It is unsuitable for prophylactic use. Close attention should be given to hygiene and to possible reservoirs of reinfection in clothing, footwear, and bedding.

Nystatin, a polyene antifungal antibiotic derived from *Streptomyces noursei*, is effective against infections caused by a wide range of yeasts and yeast-like fungi. It is poorly

absorbed from the gastrointestinal tract and is not absorbed from the skin or mucous membranes when applied topically. It is used for the treatment of candidiasis, but is less effective for prevention or treatment of candidiasis in immunocompromised patients.

Potassium iodide aqueous oral solution is a clear liquid with a characteristic strong salty taste. It is effective against sporotrichosis and subcutaneous phycomycosis, which are fungal infections caused by *Sporothrix schenckii* and *Basidiobolus haptosporus*, respectively. In subcutaneous sporotrichosis, **amphotericin B** is often effective in patients unable to tolerate iodides. **Itraconazole**, by mouth, has been tried as an alternative to potassium iodide in both cutaneous and extracutaneous sporotrichosis. In phycomycosis, **fluconazole** may be effective.

- **Ketoconazole**

- **Dosage form**

- Tablet: 200 mg

- **Uses**

- Dermatophytoses and *Malassezia* folliculitis *either* resistant to fluconazole, terbinafine, or itraconazole *or* in patients intolerant of these antifungals
 - Chronic mucocutaneous, cutaneous, and oropharyngeal candidiasis *either* resistant to fluconazole or itraconazole *or* in patients intolerant of these antifungals

- **Contraindications**

- Acute porphyria

- **Precautions**

- Predisposition to adrenocortical insufficiency
 - Hepatic impairment: Appendix E
 - Breast-feeding: Appendix C

- Pregnancy: Appendix B
- **Interactions:** Appendix A
- **Hepatotoxicity:** Potentially life-threatening hepatotoxicity reported very rarely; risk of hepatotoxicity is greater if given for more than 10 days. Monitor liver function before treatment, then at weeks 2 and 4 of treatment, then every month. Avoid or use with caution if abnormal liver function tests (avoid in active liver disease) or if history of hepatotoxicity with other drugs.

Note: Patients should be told how to recognize signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, jaundice, or dark urine develop.

○ **Dose**

- **ADULT:** 200 mg once daily, increased if response inadequate to 400 mg once daily; continue until symptoms have cleared and cultures negative, but see Precautions (max. duration of treatment 4 weeks for *Malassezia* infection)
- **CHILD,** body weight 15–30 kg: 100 mg once daily
- **CHILD,** body weight over 30 kg: Adult dose

○ **Adverse effects**

- Nausea, vomiting, abdominal pain
- Pruritus
- Less commonly diarrhea, headache, dizziness, drowsiness, and rash
- Also reported fatal liver damage (see Hepatotoxicity above), dyspepsia, raised intracranial pressure, paresthesia, adrenocortical insufficiency, erectile dysfunction, menstrual disorders, azoospermia (with high doses), gynecomastia, thrombocytopenia, photophobia, photosensitivity, and alopecia

- **Griseofulvin**

- **Dosage form**

- Tablets: 125 mg, 250 mg, and 500 mg

- **Uses**

- Fungal infections of the skin, scalp, hair, and nails where topical treatment has failed or is inappropriate

- **Contraindications**

- Severe liver disease: Appendix E
 - Pregnancy (avoid pregnancy during and for 1 month after treatment; men should not father children within 6 months of treatment):
Appendix B
 - Porphyria
 - Systemic lupus erythematosus (risk of exacerbation)

- **Precautions**

- Preexisting hepatic insufficiency (closely monitor hepatic function throughout treatment)
 - Blood disorders (monitor blood count weekly during first month of treatment)
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A

Skilled tasks: May impair ability to perform skilled tasks (such as operating machinery or driving).

- **Dose**

Superficial fungal infections, by mouth

- **ADULT:** 0.5–1 g (but not less than 10 mg/kg) daily with food in single or divided doses
- **CHILD:** 10 mg/kg daily with food in single or divided doses

Note: 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.

- **Adverse effects**

- Headache, nausea, vomiting, diarrhea, rash, dizziness, and fatigue reported
- Leukopenia, hepatotoxicity
- Sleep disturbances
- Photosensitivity
- Systemic lupus erythematosus, toxic epidermal necrolysis, erythema multiforme
- Peripheral neuropathy
- Confusion and impaired coordination

- **Nystatin**

- **Dosage form**

- Tablets: 100,000 IU and 500,000 IU
- Vaginal tablet: 100,000 IU
- Vaginal suppository: 100,000 IU per ovule
- Oral topical suspension: 100,000 IU/ml in 30 ml and 200,000 IU/ml
- Oral topical drop: 100,000 IU/ml
- Topical cream: 100,000 IU/g
- Vaginal cream: 100,000 IU/g

- **Uses**

- Oral, esophageal, intestinal, vaginal, and cutaneous candidiasis
- **Precautions**
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
- **Dose**

Oral candidiasis, by mouth

- **ADULT** and **CHILD** over 1 month: 100,000 IU after food 4 times daily usually for 7 days; continue for 48 hours after lesions have resolved

Intestinal and esophageal candidiasis, by mouth

- **ADULT:** 500,000 IU 4 times daily; continue for 48 hours after clinical cure
- **CHILD** over 1 month: 100,000 IU 4 times daily; continue for 48 hours after clinical cure

Vaginal candidiasis, vaginal administration

- **ADULT:** Insert 1–2 pessaries at night for at least 2 weeks

- **Adverse effects**
 - Nausea, vomiting, and diarrhea at high doses
 - Oral irritation and sensitization
 - Rash and rarely erythema multiforme (Stevens-Johnson syndrome)

- **Potassium iodide**

Potassium iodide is a complementary list medicine.

- **Dosage form**
 - Saturated oral solution: 1 g/ml
 - Tablet: 60 mg

- **Uses**
 - Sporotrichosis
 - Subcutaneous phycomycosis
 - Thyrotoxicosis (Section 18.8)
- **Contraindications**
 - Hypersensitivity to iodides
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Acute bronchitis or active tuberculosis
- **Precautions**
 - Addison's disease
 - Cardiac disease
 - Hyperthyroidism
 - Myotonia congenital
 - Renal impairment: Appendix D
- **Dose**

Sporotrichosis and subcutaneous phycomycosis, by mouth

- **ADULT:** Initially 1 ml 3 times daily, increased by 1 ml daily, depending on tolerance, to 10 ml daily; continue treatment for at least 4 weeks after resolution or stabilization of lesions

Note: If signs of iodism occur, suspend treatment temporarily and restart after a few days at a lower dosage.

- **Adverse effects**
 - Goiter, hypothyroidism, hyperthyroidism
 - Hypersensitivity reactions

- Iodism (characterized by metallic taste, increased salivation, coryza-like symptoms, and irritation and swelling of the eyes and usually resulting from prolonged administration)
- Also gastrointestinal disturbances and diarrhea
- Pulmonary edema, bronchitis
- Skin reactions
- Depression, insomnia, impotence, and headache reported

- **Terbinafine**

- **Dosage form**

- Tablets: 125 mg and 250 mg
- Topical cream: 1%
- Vaginal gel: 1%

- **Uses**

- Dermatophyte infections of the nails, ringworm infections (including *Tinea pedis*, *cruris*, and *corporis*) where oral therapy appropriate (due to site, severity or extent)

- **Precautions**

- Psoriasis (risk of exacerbation)
- Autoimmune disease (risk of lupus erythematosus–like effect)
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Breast-feeding: Appendix C
- Pregnancy: Appendix B

- **Dose**

By mouth

- **ADULT:** 250 mg daily usually for 2–6 weeks in *Tinea pedis*, 2–4 weeks in *Tinea cruris*, 4 weeks in *Tinea corporis*, 6 weeks–3 months in nail infections
 - **CHILD** (unlicensed): Usually for 4 weeks, *Tinea capitis*
 - **CHILD**, over 1 year, body weight 10–20 kg: 62.5 mg once daily
 - **CHILD**, body weight 20–40 kg: 125 mg once daily
 - **CHILD**, body weight over 40 kg: 250 mg once daily
- **Adverse effects**
- Abdominal discomfort, anorexia, nausea, diarrhea
 - Headache
 - Rash and urticaria occasionally with arthralgia or myalgia
 - Less commonly taste disturbance
 - Rarely liver toxicity (including jaundice, cholestasis, and hepatitis)—discontinue treatment, angioedema, dizziness, malaise, paresthesia, hypoesthesia, photosensitivity, serious skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis)—discontinue treatment if progressive skin rash
 - Very rarely psychiatric disturbances, blood disorders (including leucopenia and thrombocytopenia), lupus erythematosus–like effect, and exacerbation of psoriasis

6.4 ANTIVIRAL MEDICINES

6.4.1 Antiherpes medicines

Herpes simplex virus (HSV) infections

Aciclovir is active against herpes viruses but does not eradicate them; it is only effective if started at the onset of infection. It is also used for prevention of recurrence in the immunocompromised. Genital lesions, esophagitis, and proctitis may be treated with oral aciclovir. However, HSV encephalitis or pneumonitis should be treated with intravenous

aciclovir. Valaciclovir, a pro-drug of aciclovir, can be given by mouth as an alternative treatment for HSV infections of the skin and mucous membranes (including initial and recurrent genital herpes).

Varicella-zoster infections

Chicken pox in neonates should be treated with parenteral **aciclovir** to reduce the risk of severe disease. Otherwise, antiviral treatment is generally not required except for immunocompromised patients and those at special risk (for example, those with severe cardiovascular or respiratory disease, or a chronic skin disorder); aciclovir should be given for 10 days with at least 7 days of parenteral treatment. Specialist advice should be sought for the treatment of chicken pox during pregnancy.

While most HIV-positive patients with herpes zoster (shingles) experience only one self-limiting disease course, some will suffer repeated episodes. Treatment should be reserved for debilitating disease and when there is high risk of serious complications, such as in advanced HIV disease. Aciclovir is the treatment of choice and can be administered either orally (in high doses) or, in the case of lack of response to oral therapy or central nervous system involvement, intravenously.

Cytomegalovirus (CMV)

Parenteral antiviral ganciclovir arrests retinochoroiditis and enteritis caused by CMV in HIV-infected patients. Maintenance therapy with oral ganciclovir should be given to prevent relapse of retinitis. Alternative therapy is with intravenous foscarnet, which can be used if necessary.

6.4.2 Antiretrovirals

Also refer to *National Clinical Protocol on Anti-Retroviral Therapy (ART)*, National HIV/AIDS Control Program, MoPH Afghanistan, 2008.

Antiretroviral medicines do not cure HIV infection; they only temporarily suppress viral replication and improve symptoms. Patients receiving these drugs require careful

monitoring by appropriately trained health professionals in an adequately resourced setting. Rigorous promotion of measures to prevent new infections remains essential and this need is not diminished by the availability of antiretroviral medicines. Effective therapy requires the simultaneous use of 3 or 4 drugs; alternative regimens are necessary to meet specific requirements at start-up, substitute for first-line regimens in cases of intolerance, or replace failing regimens. The use of a 3- or 4-drug combination as specified in *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* (WHO 2013) is recommended. Fixed-dose preparations for some drug combinations are available; their use is recommended if the pharmaceutical quality is assured and interchangeability with the single products is demonstrated as specified by the relevant drug regulatory authority.

Selection of 2 or 3 protease inhibitors from the WHO Model List will need to be determined by each country after consideration of local treatment guidelines and experience, as well as comparative costs of available products. Low-dose ritonavir is used in combination with indinavir, lopinavir, or saquinavir as a “booster”; ritonavir is not recommended for use by itself.

For further information, consult documents of the National HIV/AIDS Program of Afghanistan.

Principles of treatment

Treatment is aimed at reducing the plasma viral load as much as possible and for as long as possible; it should be started preferably before the immune system is irreversibly damaged and before the onset of clinical immunodeficiency. The need for early drug treatment should, however, be balanced against the development of toxicity.

Commitment to treatment and strict adherence over many years are required; the regimen chosen should therefore take into account factors such as convenience and an individual's tolerance of various antiretrovirals. The development of resistance is reduced by using a combination of 3 or 4 drugs; such combinations should have additive or synergistic activity while ensuring that their toxicity is not additive. Women of childbearing age

receiving antiretroviral therapy should be offered effective contraceptive methods to prevent unintended pregnancy. Women who are taking non-nucleoside reverse transcriptase inhibitors or protease inhibitors, which can lower blood concentration of hormonal oral contraceptives, should be advised to use additional or alternative contraceptives.

Pregnancy

Treatment of HIV infection in pregnancy aims to:

- Minimize the viral load and disease progression in the mother
- Reduce the risk of toxicity to the fetus (although the teratogenic potential of most antiretroviral medicines is unknown)
- Prevent transmission of infection to the neonate

In pregnant women, it may be desirable to initiate antiretroviral therapy after the first trimester, although for pregnant women who are severely ill, the benefit of early therapy outweighs the potential risk to the fetus. For further information, consult documents of National HIV/AIDS Program of Afghanistan.

Breast-feeding

Antiretroviral medicines may be present in breast milk, and may reduce the viral load in breast milk, thus reducing the risk of mother-to-child transmission through breast-feeding. However, the concentration of antiretroviral medicines in breast milk may not be adequate to prevent viral replication and therefore the possibility exists of promoting the development of drug-resistant virus, which could be transmitted to the infant.

Women with HIV infection should be counseled about the risks of breast-feeding and advised, if it is possible, to avoid breast-feeding. When replacement feeding is acceptable, feasible, affordable, sustainable, and safe, breast-feeding should be avoided. Otherwise, exclusive breast-feeding is recommended during the first months of life and should then be discontinued as soon as it is feasible.

For further information, consult documents of National HIV/AIDS Program of Afghanistan.

Fixed-dose combinations

- **Atazanavir + ritonavir (ATV/RTV)**
 - **Dosage form**
 - Tablet: 300 mg + 100 mg
 - **Uses**
 - HIV infection in combination with other antiretrovirals
 - **Precautions**
 - Concurrent use with medications that may prolong the PR interval
 - Cardiac conduction disorders
 - Predisposition to prolongation of QT interval (including electrolyte disorders)
 - Concomitant use with medicines that prolong the QT interval
 - **Interactions:** Appendix A
 - **Contraindications**
 - Protease inhibitors in acute porphyria
 - **Dose**
 - HIV infection in combination with other antiretrovirals, 1 tablet once daily
 - **Adverse effects**
 - Atrioventricular blocks in children
 - Oral ulcers less common

- Cholelithiasis, hypertension, syncope, chest pain, tachypnea, peripheral neuropathy, sleep disturbances, depression, anxiety, weight change, increase of appetite, gynecomastia, renal lithiasis, hematuria, proteinuria, arthralgia, splenohepatomegaly, edema
- Palpitations
- Skin eruptions, usually in the first 3 weeks of treatment, severe skin eruptions less common and may be concomitant with systemic signs; in severe cases discontinue treatment with this drug

- **Efavirenz + emtricitabine + tenofovir**

- **Dosage form**

- Tablet: 600 mg + 200 mg + 300 mg

- **Uses**

- See each ingredient separately.

- **Emtricitabine + tenofovir**

- **Dosage form**

- Tablet: 200 mg + 300 mg

- **Uses**

- HIV infection alone as a complete regimen or in combination with other antiretroviral medicines

- **Precautions**

- See under Emtricitabine; Tenofovir

- **Dose**

HIV infection alone as a complete regimen or in combination with other antiretroviral medicines, by mouth

- **ADULT** over 18 years: 1 tablet once daily

Patient advice: Tablets can be dispersed in at least 100 mL water, orange juice, or grape juice for patients who have difficulty swallowing.

- **Adverse effects**

- *See under* Emtricitabine; Tenofovir

- **Indinavir + ritonavir**

- **Dosage form**

- Tablet: 800 mg + 100 mg

- **Indication**

- HIV infection, usually used with 2 reverse transcriptase inhibitors or a low booster dose of ritonavir

- **Contraindication**

- Porphyria

- **Precaution**

- Chronic hepatitis B or C (increased risk of hepatotoxicity)
- Hepatic impairment: Appendix E
- Ensure enough intake of water (to reduce the risk of kidney stone formation)
- Patients at risk for kidney stones (monitor for kidney stones)
- Diabetes mellitus
- Hemophilia
- Pregnancy (*see* introductory notes above on Pregnancy): Appendix A
- Breast-feeding (*see* introductory notes above on Breast-feeding) Annex C
- If administered concomitantly, it inhibits the metabolism of majority of drugs.

- **Interactions:** Appendix A

- **Dose**

HIV infection (with other antiretroviral drugs except the booster dose of ritonavir)

- **ADULT:** 800 mg indinavir and 100 mg ritonavir orally, 2 times a day

HIV infection (with other antiretroviral drugs with booster dose of ritonavir except booster dose of ritonavir)

- **ADULT:** 800 mg orally every 8 hours
- **CHILD** and **ADOLESCENT**, 4–17 years old: 500 mg every 8 hours (max. 800 mg every 8 hours); safety and effectiveness not established in children younger than 4 years

Patient recommendation: Should be taken 1 hour before or 2 hours after a meal. The drug can be taken with low-fat or light foods. There should be a 1-hour gap between taking the 2 drugs when combined with didanosine (antacids, in the composition of didanosine buffer [tablets or oral solutions], reduce the absorption of indinavir).

- **Adverse effects**

- Nausea, vomiting, diarrhea, abdominal discomfort, indigestion, bloating and intestinal gas, pancreatitis, dry mouth, impaired sense of taste
- Headache, confusion, insomnia
- Muscle pain, myositis, rhabdomyolysis, fatigue, decreased sensitivity to touch
- Paresthesia
- Hyperglycemia
- Hypersensitivity reactions, skin eruptions (including Stevens-Johnson syndrome), skin itches, dry skin, hyperpigmentation, alopecia, paronychia (inflammation of nail beds), interstitial nephritis

- Kidney stone formation (may need to postpone or stop drug; more frequent among children)
- Appearance of pus, protein, crystals, and blood in the urine and urinary urgency (in children)
- Hepatitis, transient increased blood bilirubin level
- Blood disorders including neutropenia, hemolytic anemia, and lipodystrophy, and metabolic effects (*see also* notes above)

- **Saquinavir + ritonavir**

- **Dosage form**

- Tablets: 200 mg + 500 mg

- **Uses**

- HIV infection in combination with other antiretroviral medicines

- **Precautions**

- *See* introductory notes above.
- Assess the ECG before starting treatment, then assess on day 3 or 4; if the QT interval exceeds 480 milliseconds, stop the medicines. If the QT interval is greater than 20 milliseconds above baseline or the PR interval is prolonged, using garlic capsules simultaneously with saquinavir should be avoided because garlic capsules decrease plasma concentration of saquinavir.

Note: The patient should be guided on how to understand the signs of arrhythmia; recommend seeking medical care when experiencing palpitations or syncope.

- **Contraindications**

- *See* introductory notes above.

- **Lamivudine + stavudine**

- **Dosage form**

- Tablets: 150 mg + 30 mg and 150 mg + 40 mg
 - Oral solution: 40 mg + 10 mg per 5 ml

- **Use**

- In the treatment of HIV infection in combination with other antiretroviral medicines. For further information about either of these medicines, refer to each drug separately.

- **Lamivudine + nevirapine + zidovudine**

- **Dosage form**

- Tablet: 150 mg + 200 mg + 300 mg

- **Use**

- In the treatment of HIV infection in combination with other antiretroviral medicines. For further information about either of these medicines, refer to each drug separately.

- **Stavudine + lamivudine + nevirapine**

- **Dosage form**

- Tablet: 30 mg + 150 mg + 200 mg

- **Uses**

- HIV infection alone as a complete regimen or in combination with other antiretroviral medicines.

- **Precautions**

- *See under* Lamivudine; Nevirapine; Stavudine
 - Combined preparation not suitable for use in children

- **Dose**

HIV infection alone as a complete regimen or in combination with other antiretroviral medicines, by mouth

- **ADULT:** 1 tablet twice daily

Note: A lead-in dose of nevirapine, 200 mg once daily for 14 days, is recommended for those who have just initiated therapy with nevirapine; the other drugs should be taken separately during this time. This twice-daily fixed-dose combination tablet can then be started as long as there are no rash or liver function test abnormalities present (*see under* Precautions for nevirapine). If treatment with the fixed-dose combination tablet is interrupted for more than 7 days, reintroduce using a lead-in dose of nevirapine, 200 mg daily, and separate tablets for the other medicines.

- **Adverse effects**

- *See under* Lamivudine; Nevirapine; Stavudine

6.4.2.1 Nucleoside/nucleotide reverse transcriptase inhibitors

- **Abacavir**

- **Dosage form**

- Tablet: 300 mg (as sulfate)

- **Uses**

- HIV infection in combination with at least 2 other antiretroviral medicines

- **Precautions**

- Chronic hepatitis B or C
- Hepatic impairment (*see note on* Hepatic disease below): Appendix E

- Renal impairment: Appendix D
- Pregnancy (*see* introductory note above): Appendix B
- Breast-feeding (*see* introductory note above): Appendix C
- **Interactions:** Appendix A
- **Hypersensitivity reactions:** Life-threatening hypersensitivity reactions characterized most commonly by fever or rash and possibly nausea, vomiting, diarrhea, abdominal pain, dyspnea, cough, lethargy, malaise, headache, and myalgia; less frequently by mouth ulceration, edema, hypotension, sore throat, adult respiratory distress syndrome, paresthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia, renal failure, and anaphylaxis; and rarely by myolysis have been reported. Laboratory abnormalities may include raised liver enzymes (*see* Hepatic disease 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); also discontinue if hypersensitivity cannot be ruled out, even when other diagnoses possible (if rechallenge is necessary, it must be carried out in a 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 is needed with concomitant use of drugs that are known to cause skin toxicity.

Patient advice: Patients should be told about 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 re-starting treatment.

Hepatic disease: Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis have been reported. Exercise caution in patients

(particularly obese women) with hepatomegaly, hepatitis, 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 hyperlactatemia, progressive hepatomegaly, or lactic acidosis occurs.

- **Dose**

HIV infection in combination with at least 2 other antiretroviral medicines, by mouth

- **ADULT:** 300 mg twice daily
- **CHILD** 3 months–16 years: 8 mg/kg twice daily (max. 600 mg daily)

- **Adverse effects**

- Hypersensitivity reactions including nausea, vomiting, diarrhea, anorexia, lethargy, fatigue, fever, headache, insomnia, and dizziness (*see also* note on Hypersensitivity reactions above)
- Blood disorders
- Lipodystrophy (*see* introductory note above)
- Pancreatitis, liver damage, and lactic acidosis (*see* note on Hepatic disease above)
- Very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis
- Rash and gastrointestinal disturbances more common in children

- **Delavirdine**

- **Dosage form**

- Tablet: 200 mg (as mesylate)

- **Use**

- HIV infection in combination with other medicines

- **Contraindications**

- Taking delavirdine is contraindicated with drugs that are dependent on CYP3A4 for their excretion from the body, because its high concentration in plasma is associated with severe fatal cases. These drugs include antihistamines (terfenadine), ergot derivatives, cisapride, sedative and hypnotic medicines (alprazolam and midazolam), anti-epileptic carbamazepine (phenytoin and phenobarbital), and antimycobacterial drugs (rifabutin and rifampicin).

- **Precautions**

- Discontinue in case of severe skin eruptions or eruptions associated with fever, blisters, mouth ulcers, conjunctivitis, swelling, muscle or joint pain.
- The drug should be prescribed with caution to patients with known liver function disorders.
- Pregnancy: Appendix B

- **Dose**

- Usual dose of 400 mg 3 times a day
- **Interactions:** Appendix A

- **Adverse effects**

- Common adverse effects of delavirdine include skin eruptions, which appear during the first 3 months of treatment and heal within 3–14 days; severe skin reactions including erythema multiforme and Stevens-Johnson syndrome have been reported.
- Other severe or moderate side effects include abdominal pain, weakness, malaise, fever, headache, cold- or flu-like symptoms, and localized pain.
- Other reported side effects include gastrointestinal disorders (diarrhea, nausea, vomiting), increased liver enzyme levels, anxiety, symptoms of depression, insomnia, and respiratory symptoms (pharyngitis, sinusitis,

and upper respiratory tract infections); renal failure, hemolytic anemia, rhabdomyolysis, and acute renal failure also reported.

- **Emtricitabine**

- **Dosage form**

- Tablet: 200 mg
 - Combination tablet: emtricitabine + tenofovir + efavirenz (200 mg + 300 mg + 600 mg)
 - Combination tablet: Emtricitabine + tenofovir (200 mg + 300 mg)
 - Oral liquid: 50 mg/5 ml

Note: Where appropriate, capsules may be used instead of oral solution. Oral solution contains propylene glycol as an excipient.

- **Uses**

- HIV infection in combination with at least 2 other antiretroviral medicines

- **Precautions**

- See notes below.
 - Hepatitis B infection (risk of exacerbation)
 - Renal impairment: Appendix D
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A
 - **Hepatic disease:** 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); discontinue if rapid deterioration in liver function tests, symptomatic hyperlactatemia, progressive hepatomegaly or

lactic acidosis occurs. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of emtricitabine

- **Dose**

HIV infection by mouth

- **ADULT** and **CHILD**: Over 33 kg, 1 capsule (200 mg) with tenofovir 300 mg once daily

- **Adverse effects**

- Nausea, vomiting, abdominal pain, dyspepsia, diarrhea
- Headache, dizziness, peripheral neuropathy, asthenia, insomnia, abnormal dreams, depression
- Anemia, neutropenia
- Arthralgia, myalgia, bone necrosis
- Raised serum lipase, amylase, creatine kinase, and liver enzymes (*see also* note on Hepatic disease above), hyperbilirubinemia, hypertriglyceridemia, hyperglycemia
- Rash, pruritus, urticaria, hyperpigmentation
- Lipodystrophy and metabolic effects

- **Lamivudine**

- **Dosage form**

- Tablet: 100 mg, 150 mg, and 300 mg (as sulfate)
- Oral suspension: 50 mg/5 ml

- **Uses**

- HIV infection in combination with at least 2 other antiretroviral medicines
- Prevention of mother-to-child HIV transmission
- Treatment of hepatitis B infection

- **Contraindications**

- Peripheral neuropathy
- Muscular disorders including rhabdomyolysis, nasal symptoms and alopecia
- **Interactions:** Appendix A
- **Caution:** Recurrent hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine. While under treatment for hepatitis B infection, the liver function should be monitored every 3 months; viral load and serological markers for hepatitis B virus every 3–6 months and in case of liver replacement every year should be monitored.
- **Hepatic disease:** 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 hyperlactatemia, progressive hepatomegaly, or lactic acidosis occurs. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine.

○ **Dose**

HIV infection (in combination with other antiretroviral medicines), by mouth

- **ADULT:** 150 mg twice daily or 300 mg once daily
- **INFANT** under 1 month: 2 mg/kg twice daily
- **CHILD** 1 month or over: 4 mg/kg twice daily (max. 300 mg daily)

Prevention of mother-to-child transmission of HIV (see also introductory note above under Pregnancy), by mouth

- **ADULT:** 150 mg at onset of labor followed by 150 mg every 12 hours until delivery; after delivery, 150 mg twice a day for 7 days

- **Adverse effects**
 - Nausea, vomiting, diarrhea, abdominal pain
 - Cough
 - Headache, fatigue, insomnia
 - Malaise, fever, rash, alopecia, muscle disorders
 - Nasal symptoms
 - Peripheral neuropathy reported
 - Rarely pancreatitis (discontinue)
 - Neutropenia, anemia, thrombocytopenia and red cell aplasia
 - Lactic acidosis
 - Raised liver enzymes and serum amylase reported
- **Tenofovir**
 - **Dosage form**
 - Tablet: 300 mg
 - **Uses**
 - HIV infection in combination with other antiretroviral medicines
 - Chronic hepatitis B infection with *either* compensated liver disease (with evidence of viral replication, and histologically documented active liver inflammation or fibrosis) *or* decompensated liver disease
 - **Precautions**
 - Renal impairment: Appendix D
 - Hepatic disease (*see note below*)
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - ***Interactions:*** Appendix A
 - ***Hepatic disease:*** 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 hyperlactatemia, progressive hepatomegaly, or lactic acidosis occurs. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of tenofovir.

- **Dose**

HIV infection (in combination with other antiretroviral medicines), by mouth

- **ADULT:** 1 tablet once daily

Patient advice: Tablets can be dispersed in at least 100 ml water, orange juice, or grape juice for patients with difficulty swallowing.

- **Adverse effects**

- Nausea, vomiting, abdominal pain, flatulence, diarrhea, anorexia
- Hypophosphatemia
- Dizziness, peripheral neuropathy, headache, dyspnea, insomnia, depression, asthenia, sweating, myalgia, rash, hypertriglyceridemia, hyperglycemia, 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

- **Zidovudine**

Also known as azidothymidine

- **Dosage form**

- Tablets and capsules: 100 mg, 250 mg, and 300 mg
- Oral suspension: 50 mg/5 ml
- Infusion solution: 10 mg/ml in 20 ml ampoule

Note: The abbreviation AZT, which has sometimes been used for zidovudine, has also been used for another medicine.

- **Uses**

- HIV infection in combination with at least two other antiretroviral medicines
- Prevention of mother-to-child HIV transmission

- **Contraindications**

- Abnormally low neutrophil counts or hemoglobin (consult product literature)
- Neonates with either hyperbilirubinemia requiring treatment other than phototherapy or raised transaminase (consult product literature)

- **Precautions**

- Hematological toxicity
- Vitamin B12 deficiency (increased risk of neutropenia)
- Anemia or myelosuppression (reduce dose or interrupt treatment according to product literature)
- Renal impairment: Appendix D
- Chronic hepatitis B or C
- Hepatic impairment (see note on Hepatic disease below): Appendix E
- Elderly

- Pregnancy (*see* introductory note above): Appendix B
- Breast-feeding (*see* introductory note above): Appendix C
- **Interactions:** Appendix A
- **Hepatic disease:** Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis have been reported. Exercise caution in patients (particularly obese women) with hepatomegaly, hepatitis, 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 hyperlactatemia, progressive hepatomegaly, or lactic acidosis occurs.

○ **Dose**

HIV infection (in combination with other antiretroviral medicines), by mouth

- **ADULT:** 500–600 mg daily in 2–3 divided doses
- **INFANT** under 4 weeks: 4 mg/kg twice daily
- **CHILD** 4 weeks–13 years: 180 mg/m² twice daily

HIV infection in patients temporarily unable to take zidovudine by mouth, by intravenous infusion, over 1 hour

- **ADULT:** 1–2 mg/kg every 4 hours (approximating to 1.5–3 mg/kg every 4 hours by mouth) usually for not more than 2 weeks
- **CHILD** 3 months–12 years: 80–160 mg/m² every 6 hours (120 mg/m² every 6 hours approximates to 180 mg/m² every 6 hours by mouth)

Prevention of mother-to-child transmission of HIV (see also introductory note above under Pregnancy), by mouth

- **ADULT:** 300 mg twice daily from week 28 of pregnancy; 600 mg at onset of labor (or 300 mg at onset of labor, followed by 300 mg every 3 hours until delivery); 300 mg twice daily after delivery for 7 days

- **NEONATE:** 4 mg/kg every 12 hours starting within 12 hours of birth for up to 1–6 weeks depending on national recommendations

Prevention of mother-to-child transmission of HIV (see also introductory note above under Pregnancy), by intravenous infusion

- **NEONATE:** 1.5 mg/kg every 6 hours until oral dosing possible

Administration and dilution: According to manufacturer's directions

○ **Adverse effects**

- Anemia (may require transfusion), neutropenia, and leukopenia (all more frequent with high dose and advanced disease)
- Also nausea and vomiting, abdominal pain, dyspepsia, diarrhea, flatulence, taste disturbance, pancreatitis, liver disorders including fatty change and raised bilirubin and liver enzymes (*see note on Hepatic disease above*)
- Chest pain, dyspnea, cough
- Influenza-like symptoms, headache, fever, paresthesia, neuropathy, convulsions, dizziness, somnolence, insomnia, anxiety, depression, loss of mental acuity, malaise, anorexia, asthenia, myopathy, myalgia
- Pancytopenia, thrombocytopenia
- Gynecomastia
- Urinary frequency
- Rash, pruritus
- Pigmentation of nail, skin, and oral mucosa

6.4.2.2 *Non-nucleoside reverse transcriptase inhibitors*

- **Efavirenz**

- **Dosage form**

- Tablets and capsules: 50 mg, 100 mg, 200 mg, and 600 mg
 - Oral ingestion liquid: 150 mg/5 ml; also available in combination with tenofovir + emtricitabine

- **Uses**

- HIV infection in combination with at least 2 other antiretroviral medicines

- **Contraindications**

- Not to be used in acute porphyria
 - Pregnancy: substitute nevirapine for efavirenz in pregnant women or women for whom effective contraception cannot be assured

- **Precautions**

- The elderly
 - History of mental illness or seizures
 - Pregnancy: Appendix B
 - Hepatic impairment (avoid if severe): Appendix E
 - Severe renal impairment: Appendix D
 - Breast-feeding: Appendix C
 - Chronic hepatitis B or C
 - **Interactions:** Appendix A
 - **Rash:** Rash, usually occurring in the first 2 weeks, is the most common adverse effect; discontinue if rash is severe or if rash is accompanied by blistering, desquamation, mucosal involvement or fever; if rash is mild or moderate, continue without interruption (rash usually resolves within 1 month).

- **Psychiatric disorders:** Patients should be advised to seek medical attention if severe, depression, psychosis, or suicidal ideation occurs.

- **Dose**

HIV infection (in combination with other antiretroviral medicines), by mouth (as tablets or capsules)

- **ADULT:** 600 mg once daily or 300 mg twice daily

Missed dose: 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.

- **Adverse effects**

- Rash including Stevens-Johnson syndrome
- Abdominal pain, diarrhea, nausea, vomiting
- Anxiety, depression, dizziness, headache, insomnia, somnolence, abnormal dreams, fatigue, impaired concentration (administration at bedtime especially in the first 2–4 weeks reduces central nervous system effects)
- Pruritus
- Less frequently hepatitis, psychosis, mania, suicidal ideation, amnesia, ataxia, convulsions, and blurred vision
- Raised serum cholesterol, elevated liver enzymes, pancreatitis, gynecomastia, lipodystrophy syndrome, and photosensitivity also reported

- **Etravirine**

- **Dosage form**

- Tablet: 25 mg

- **Uses**

- In combination with other antiretroviral drugs (including a boosted protease inhibitor) for HIV infection resistant to other non-nucleoside reverse transcriptase inhibitors and protease inhibitors
- **Contraindications**
 - Acute porphyria
- **Precautions**
 - **Interactions:** Appendix A
 - **Hypersensitivity reactions:** Rash, usually in the second week, is the most common side effect and appears more frequently in women. Life-threatening hypersensitivity reactions reported usually during week 3–6 of treatment and characterized 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.

Note: Patients should be told how to recognize hypersensitivity reactions and advised to seek immediate medical attention if hypersensitivity reaction or severe rash develops.

- **Dose**
 - **ADULT** over 18 years: 200 mg twice daily after food

Missed dose: 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.

- **Adverse effects**

- Rash (including Stevens-Johnson syndrome rarely and toxic epidermal necrolysis very rarely; *see also* Hypersensitivity reactions above)
- Gastro-esophageal reflux, nausea, abdominal pain, flatulence, gastritis
- Myocardial infarction, hypertension
- Peripheral neuropathy
- Diabetes, hyperlipidemia, also lipodystrophy syndrome
- Renal failure
- Anemia
- Less commonly pancreatitis, hematemesis, hepatitis, angina, bronchospasm, drowsiness, malaise, gynecomastia, blurred vision, dry mouth, and sweating
- Also reported osteonecrosis, hemorrhagic stroke, and hypersensitivity reactions

- **Nevirapine**

- **Dosage form**

- Tablet: 200 mg
- Oral liquid: 50 mg/5 ml

- **Uses**

- HIV infection in combination with at least 2 other antiretroviral medicines
- Prevention of mother-to-child HIV transmission

- **Contraindications**

- Severe hepatic impairment
- Post-exposure prophylaxis

- **Precautions**

- Hepatic impairment (*see note below*): Appendix E
- Chronic hepatitis B or C, high CD4 cell count, and women (greater risk of hepatic side effects—preferably avoid in women with a CD4 cell count

greater than 250 cells/mm³ and in men with a CD4 cell count greater than 400 cells/mm³

- Pregnancy (*see* introductory note above): Appendix B
- Breast-feeding (*see* introductory note above): Appendix C
- **Interactions:** Appendix A
- **Hepatic disease:** Potentially life-threatening hepatotoxicity, including fatal fulminant hepatitis, reported usually occurring in the first 6 weeks. Close monitoring is 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 are accompanied by hypersensitivity reactions (for example, rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, and granulocytopenia). If severe liver abnormalities occur without hypersensitivity reactions, suspend, but discontinue permanently if significant liver function abnormalities recur. Monitor patient closely if there are mild-to-moderate liver abnormalities with no hypersensitivity reactions.
- **Rash:** Rash, usually occurring in first 6 weeks, is the most common side effect; incidence can be reduced if introduced at low dose and dose increased gradually. Monitor closely for skin reactions during first 18 weeks; discontinue permanently if rash is severe or if rash is accompanied by blistering, oral lesions, conjunctivitis, facial edema, general malaise, or hypersensitivity reactions; if rash is mild or moderate, continue without interruption but dose should not be increased until rash resolves.

Note: If treatment is interrupted for more than 7 days, reintroduce at a low dose and increase dose cautiously.

Patient advice: Patients should be told 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.

○ **Dose**

HIV infection (in combination with other antiretroviral medicines), by mouth

- **ADULT:** 200 mg once daily for first 14 days, then (if no rash present) 200 mg twice daily
- **INFANT** 15–30 days old: 5 mg/kg once daily for 14 days, then (if no rash present) 120 mg/m² twice daily for 14 days, then 200 mg/m² twice daily
- **CHILD** 1 month–13 years: 120 mg/m² once daily for first 14 days, then (if no rash present) 120–200 mg/m² twice daily

Prevention of mother-to-child transmission of HIV (see also introductory note above under Pregnancy), by mouth

- **ADULT:** 200 mg as a single dose at onset of labor
- **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: In adults, if treatment is interrupted for more than 7 days, reintroduce at a dose of 200 mg daily (**INFANT** 15–30 days old: 5 mg/kg; **CHILD** over 1 month: 120 mg/m²) and increase dose cautiously.

○ **Adverse effects**

- Rash including Stevens-Johnson syndrome and rarely, toxic epidermal necrolysis
- Nausea, hepatitis (*see also* Hepatic disease above), headache
- Less commonly vomiting, abdominal pain, fatigue, fever, and myalgia

- Rarely diarrhea, angioedema, anaphylaxis, hypersensitivity reactions (may involve hepatic reactions and rash; *see* Hepatic disease above)
- Arthralgia, anemia, and granulocytopenia (more frequent in children)
- Very rarely neuropsychiatric reactions

6.4.2.3 *Protease inhibitors*

- **Entecavir**

- **Dosage form**

- Tablet: 0.5 mg

- **Uses**

- Chronic hepatitis B infection with compensated liver disease, evidence of viral replication, and histologically documented active liver inflammation or fibrosis

- **Precautions**

- Monitor liver function tests every 3 months, and viral and serological 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).
- HIV infection—risk of HIV resistance in patients not receiving highly active antiretroviral therapy
- Lamivudine-resistant chronic hepatitis B—risk of entecavir resistance
- Discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.
- Breast-feeding: Appendix C
- Pregnancy: Appendix B
- **Renal impairment:** Reduce dose if eGFR less than 50 ml/min/1.73 m²

- **Dose**

- **ADULT** over 18 years: not previously treated with nucleoside analogues, 500 micrograms once daily
- **ADULT** over 18 years with lamivudine-resistant chronic hepatitis B: 1 mg once daily; consider other treatment if inadequate response after 6 months

Patient advice: Take at least 2 hours before or 2 hours after food.

- **Adverse effects**

- Nausea, vomiting, dyspepsia, diarrhea, raised serum amylase and lipase, headache, fatigue, dizziness, sleep disturbances
- Less commonly thrombocytopenia, rash, alopecia

- **Indinavir**

- **Dosage form**

- Tablets: 200 mg, 333 mg, and 400 mg (as sulfate); also in combination indinavir 800 mg + ritonavir 100 mg

- **Uses**

- HIV infection usually in combination with two nucleoside reverse transcriptase inhibitors and a low-dose ritonavir booster

- **Contraindication**

- Porphyria

- **Precautions**

- Chronic hepatitis B or C (increased risk of hepatotoxicity)
- Hepatic impairment: Appendix E
- Ensure adequate hydration (to reduce risk of nephrolithiasis)
- Patients at risk of nephrolithiasis (monitor for nephrolithiasis)

- Diabetes mellitus (*see also* introductory notes above under Lipodystrophy and metabolic effects)
- Hemophilia
- Pregnancy (*see* introductory note above): Appendix B
- Breast-feeding (*see* introductory note above): Appendix C
- Metabolism of many drugs inhibited if administered concomitantly
- **Interactions:** Appendix A

○ **Dose**

HIV infection (in combination with other antiretroviral medicines and a ritonavir booster), by mouth

- **ADULT:** Indinavir, 800 mg, and ritonavir, 100 mg, both twice daily

HIV infection (in combination with other antiretroviral medicines but without a ritonavir booster), by mouth

- **ADULT:** 800 mg every 8 hours
- **CHILD** and **ADOLESCENT** 4–17 years: 500 mg/m² every 8 hours (max. 800 mg every 8 hours)
- **CHILD** under 4 years: Safety and efficacy not established

Patient advice: Administer 1 hour before or 2 hours after a meal; may be administered with a low-fat, light meal. When given in combination with didanosine, allow 1 hour between the drugs (antacids in buffered formulations of didanosine [tablets and oral solution] reduce absorption of indinavir).

○ **Adverse effects**

- Nausea, vomiting, diarrhea, abdominal discomfort, dyspepsia, flatulence, pancreatitis, dry mouth, taste disturbances
- Headache, dizziness, insomnia
- Myalgia, myositis, rhabdomyolysis, fatigue, hypoesthesia, paresthesia

- Hyperglycemia
- Hypersensitivity reactions, rash (including Stevens-Johnson syndrome), pruritus, dry skin, hyperpigmentation, alopecia, paronychia
- Interstitial nephritis, nephrolithiasis (may require interruption or discontinuation; more frequent in children), dysuria, hematuria, crystalluria, proteinuria, pyuria (in children)
- Hepatitis, transient hyperbilirubinemia
- Blood disorders including neutropenia, and haemolytic anemia
- Lipodystrophy and metabolic effects (*see also* introductory note above)

- **Lopinavir + ritonavir**

- **Dosage form**

- Capsules: 133.3 mg + 33.3 mg and 200 mg + 50 mg
- Oral liquid: 400 mg + 100 mg/5 ml

Note: 5 ml oral solution = 3 capsules (133.3 mg + 33.3 mg); where appropriate, capsules may be used instead of oral solution. Oral solution excipients include propylene glycol and alcohol, 42%.

- **Uses**

- HIV infection in combination with at least two other antiretroviral medicines

Note: Ritonavir increases the effect of lopinavir; the low dose in this combination does not have intrinsic antiviral activity.

- **Precautions**

- Chronic hepatitis B or C (increased risk of hepatotoxicity), hepatic impairment (avoid if severe): Appendix E
- Renal impairment: Appendix D
- Hemophilia

- Pregnancy (*see* introductory note above): Appendix B
- Breast-feeding (*see* introductory note above): Appendix C
- Diabetes mellitus
- Oral solution contains propylene glycol—avoid in hepatic and renal impairment, and in pregnancy, increased susceptibility to propylene glycol toxicity in slow metabolizers.
- Concomitant use with drugs that prolong QT interval
- **Interactions:** Appendix A
- **Pancreatitis:** Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated; discontinue if pancreatitis is diagnosed.

○ **Dose**

HIV infection (in combination with other antiretroviral medicines), by mouth

- **ADULT** and **ADOLESCENT** with body surface area of 1.3 m² or greater: 3 capsules or 5 ml twice daily (lopinavir 400 mg + ritonavir 100 mg, twice daily)
- **CHILD** 6 months–13 years: Lopinavir 225 mg/m² + ritonavir 56.25 mg/m² twice daily (or body weight 7–15 kg: lopinavir 12 mg/kg + ritonavir 3 mg/kg twice daily; body weight 15–40 kg: lopinavir 10 mg/kg + ritonavir 2.5 mg/kg twice daily)

Note: Increase dose by 33% if used in combination with efavirenz or with nevirapine.

Patient advice: Each dose to be taken with food.

○ **Adverse effects**

- Gastrointestinal disturbances, anorexia

- Hepatic dysfunction, pancreatitis (*see* note above)
- Blood disorders (including anemia, neutropenia, and thrombocytopenia), sleep disturbances, fatigue, headache, dizziness, paresthesia
- Myalgia, myositis, rhabdomyolysis
- Taste disturbances
- Rash, pruritus, Stevens-Johnson syndrome, hypersensitivity reactions
- Lipodystrophy and metabolic effects (*see also* introductory note above)
- Electrolyte disturbances in children
- Less commonly dysphagia, appetite changes, weight changes, cholecystitis, hypertension, myocardial infarction, palpitation, thrombophlebitis, vasculitis, chest pain, edema, dyspnea, cough, agitation, anxiety, amnesia, ataxia, hypertonia, confusion, depression, abnormal dreams, extrapyramidal effects, neuropathy, influenza-like syndrome, Cushing's syndrome, hypothyroidism, menorrhagia, sexual dysfunction, breast enlargement, dehydration, hypercalciuria, lactic acidosis, arthralgia, hyperuricemia, abnormal vision, otitis media, tinnitus, dry mouth, sialadenitis, mouth ulceration, periodontitis, acne, alopecia, dry skin, sweating, skin discoloration, and nail disorders
- Rarely prolonged PR interval

- **Nelfinavir**

- **Dosage form**

- Oral ingestion powder: 50 mg/g
 - Tablets: 250 mg and 625 mg (as mesilate)
 - Oral ingestion suspension: 200 mg/5 ml

- **Uses**

- HIV infection in combination with at least two other antiretroviral medicines

- **Precautions**

- Renal impairment: Appendix E
- Hepatic impairment, chronic hepatitis B or C (increased risk of hepatotoxicity)
- Diabetes mellitus
- Hemophilia
- Pregnancy (*see* introductory note above): Appendix B
- Breast-feeding (*see* introductory note above): Appendix C
- **Interactions:** Appendix A

○ **Dose**

HIV infection (in combination with other antiretroviral medicines), by mouth

- **ADULT:** 1.25 g twice daily or 750 mg 3 times daily
- **CHILD** under 1 year: 65–75 mg/kg twice daily or 40–50 mg/kg 3 times daily
- **CHILD** 1–13 years: 55–65 mg/kg twice daily

Patient advice: Administer with or after food; powder may be mixed with water, milk, formula feeds or pudding; it should not be mixed with acidic foods or juices owing to its taste.

○ **Adverse effects**

- Diarrhea, nausea, vomiting, flatulence, abdominal pain
- Rash (very rarely erythema multiforme)
- Reports of elevated creatine kinase, hepatitis, pancreatitis, neutropenia, and hypersensitivity reactions (including bronchospasm, fever, pruritus, and facial edema)
- Myalgia, myositis, and rhabdomyolysis
- Lipodystrophy and metabolic effects (*see also* introductory note above)

- **Raltegravir**

- **Dosage form**

- Tablet: 400 mg (as potassium)

- **Uses**

- HIV infection in combination with other antiretroviral drugs

- **Precautions**

- Risk factors for myopathy or rhabdomyolysis
 - Chronic hepatitis B or C (greater risk of hepatic side effects)
 - Psychiatric illness (may exacerbate underlying illness, including depression)
 - Hepatic impairment: Appendix E
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A

- **Dose**

- **ADULT:** 400 mg twice daily by mouth
 - **CHILD** 16–18 years: 400 mg twice daily by mouth

- **Adverse effects**

- Diarrhea, nausea, vomiting, abdominal pain, flatulence, hypertriglyceridemia, dizziness, headache, insomnia, abnormal dreams, asthenia, rash (Stevens-Johnson syndrome reported)
 - Less commonly gastritis, hepatitis, pancreatitis, dry mouth, gastro-esophageal reflux, taste disturbances, pain on swallowing, peptic ulcer, constipation, rectal bleeding, lipodystrophy (metabolic effects associated with antiretroviral treatment include fat redistribution, insulin resistance,

and dyslipidemia; collectively, these have been termed lipodystrophy syndrome)

- The usual risk factors for cardiovascular disease should be taken into account before starting antiretroviral therapy and patients should be advised about lifestyle changes to reduce their cardiovascular risk.
- Plasma lipids and blood glucose should be measured before starting antiretroviral therapy, after 3–6 months of treatment, and then annually.
- Fat redistribution (with loss of subcutaneous fat, increased abdominal fat, “buffalo hump” and breast enlargement) is associated with regimens containing protease inhibitors and nucleoside reverse transcriptase inhibitors.
- Stavudine (especially in combination with didanosine), and to a lesser extent zidovudine, are associated with a higher risk of lipodystrophy and should be used only if alternative regimens are not suitable.
- Dyslipidemia is associated with antiretroviral treatment, particularly with protease inhibitors. Protease inhibitors and some nucleoside reverse transcriptase inhibitors are associated with insulin resistance and hyperglycemia. Of the protease inhibitors, atazanavir and darunavir may be less likely to cause dyslipidemia, while saquinavir and atazanavir may be less likely to impair glucose tolerance); other adverse effects may include palpitation, ventricular extrasystoles, bradycardia, hypertension, flushing, chest pain, edema, dysphonia, epistaxis, nasal congestion, drowsiness, anxiety, appetite changes, confusion, impaired memory and attention, depression, pyrexia, chills, carpal tunnel syndrome, tremor, peripheral neuropathy, erectile dysfunction, gynecomastia, menopausal symptoms, osteopenia, renal failure, nocturia, polydipsia, anemia, thrombocytopenia, neutropenia, arthralgia, myalgia, rhabdomyolysis, visual disturbances, tinnitus, gingivitis, glossitis, acne, pruritus, hyperhidrosis, dry skin, skin papilloma, and alopecia.

- *See also* Osteonecrosis. (Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.)

- **Ritonavir**

- **Dosage form**

- Tablet: 100 mg
- Oral liquid: 400 mg/5 ml

- **Uses**

- HIV infection, as a booster to increase the effect of indinavir, lopinavir, or saquinavir, in combination with at least 2 other antiretroviral medicines.

- **Contraindications**

- Severe hepatic impairment
- Porphyria

- **Precautions**

- Chronic hepatitis B or C (increased risk of hepatotoxicity)
- Hepatic impairment: Appendix E
- Diabetes mellitus
- Hemophilia
- Pregnancy (see introductory note above): Appendix B
- Breast-feeding (see introductory note above): Appendix C
- **Interactions:** Appendix A
- **Pancreatitis:** Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated; discontinue if pancreatitis is diagnosed.

- **Dose**

HIV infection (as a booster with other antiretroviral medicines), by mouth

- **ADULT:** 100 mg twice daily
- **CHILD** 6 months–13 years: 57.5 mg/m² twice daily or 3–5 mg/kg twice daily (max. 100 mg twice daily)

○ **Adverse effects**

- Nausea, vomiting, diarrhea (may impair absorption—close monitoring required), abdominal pain, taste disturbances, dyspepsia, anorexia, throat irritation
- Vasodilatation, hypotension, syncope
- Headache, drowsiness
- Circumoral and peripheral paresthesia, hyperesthesia, 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, anemia, neutropenia, and increased prothrombin time
- Pancreatitis (*see also* note on Pancreatitis above)
- Lipodystrophy and metabolic effects (*see also* introductory note above)

• **Saquinavir**

○ **Dosage form**

- Capsule: 200 mg

○ **Uses**

- HIV infection in combination with at least 2 other antiretroviral medicines and usually a low-dose ritonavir booster

- **Contraindications**

- Severe hepatic impairment: Appendix E

- **Precautions**

- Chronic hepatitis B or C
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Diabetes mellitus
- Hemophilia
- Pregnancy (*see* introductory note above): Appendix B
- Breast-feeding (*see* introductory note above): Appendix C
- Concomitant use of garlic (reduces plasma saquinavir concentration)
- **Interactions:** Appendix A

- **Dose**

HIV infection (in combination with other antiretroviral medicines and a ritonavir booster), by mouth

- **ADULT:** 1 g saquinavir and 100 mg ritonavir, twice daily

HIV infection (in combination with other antiretroviral medicines but without a ritonavir booster), by mouth

- **ADULT:** 1.2 g every 8 hours after a meal
- **CHILD** under 16 years: Safety and efficacy not established

Patient advice: Take with or after food.

- **Adverse effects**

- Diarrhea, buccal and mucosal ulceration, abdominal discomfort, nausea, vomiting, taste disturbances

- Headache, chest pain, peripheral neuropathy, paresthesia, dizziness, insomnia, mood changes, changes in libido, ataxia, musculoskeletal disorders, fatigue
- Hypersensitivity reactions, fever, pruritus, rash, and other skin eruptions
- Rarely Stevens-Johnson syndrome
- Thrombocytopenia and other blood disorders
- Liver damage, pancreatitis and nephrolithiasis
- Reports of elevated creatine kinase, raised liver enzymes and neutropenia when used in combination therapy
- Lipodystrophy and metabolic effects (*see also* introductory note above)

- **Fosamprenavir + ritonavir**

- **Dosage form**

- Tablet: 700 mg + 100 mg

- **Indication**

- HIV infection in combination with other antiretroviral drugs

- **Precaution**

- Rash may occur, usually in second week of treatment, which should be discontinued permanently if severe rash with systemic or allergic symptoms or mucosal involvement occurs. If rash is mild or moderate, may continue without interruption, usually resolves within 2 weeks and may respond to antihistamines.
- **Interaction:** Appendix A

- **Contraindications**

- Protease inhibitors should not be used in acute porphyria.
- **Hepatic failure:** Protease inhibitors should be used with caution in chronic hepatitis B and C patients due to the risk of hepatic side effects. The manufacturers recommend caution in mild hepatitis. In moderate cases,

the dose should be decreased to 450 mg twice daily and in severe cases to 300 mg twice daily.

- **Dose**
 - 2 tablets daily
- **Adverse effects**
 - Skin rashes
 - Rarely Stevens-Johnson syndrome

6.4.3 Other antivirals

- **Enfuvirtide**
 - **Dosage form**
 - Tablet: 180 mg
 - **Uses**
 - HIV infection in combination with other antiretroviral drugs for resistant infection or for patients intolerant to other antiretroviral regimens
 - **Precautions**
 - Hypersensitivity reactions including rash, fever, nausea, vomiting, chills, rigors, low blood pressure, respiratory distress, glomerulonephritis, and raised liver enzymes reported
 - Discontinue immediately if any signs or symptoms of systemic hypersensitivity develop and do not rechallenge
 - Hepatic impairment: Appendix E
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C

Patient advice: Patients should be told how to recognize signs of hypersensitivity, and advised to discontinue treatment and seek immediate medical attention if symptoms develop.

- **Dose**

By subcutaneous injection

- **ADULT:** 90 mg twice daily

- **Indication and dose for children**

For HIV infection in combination with other antiretroviral drugs for resistant infection or for children intolerant to other antiretroviral regimens, by subcutaneous injection

- **CHILD** 6–16 years: 2 mg/kg (max. 90 mg) twice daily
- **CHILD** 16–18 years: 90 mg twice daily

Patient advice: Patients or carers should be told how to recognize signs of hypersensitivity, and advised to discontinue treatment and seek immediate medical attention if symptoms develop.

- **Adverse effects**

- Injection-site reactions
- Pancreatitis, gastro-esophageal reflux disease, anorexia, weight loss
- Hypertriglyceridemia
- Peripheral neuropathy, asthenia, tremor, anxiety, nightmares, irritability, impaired concentration, vertigo
- Pneumonia, sinusitis, influenza-like illness
- Diabetes mellitus
- Hematuria
- Renal calculi, lymphadenopathy

- Myalgia
- Conjunctivitis
- Dry skin, acne, erythema, skin papilloma
- Less commonly hypersensitivity reactions (*see* Cautions)
- *See also* Osteonecrosis (osteonecrosis has been reported in patients with advanced HIV disease or following long term exposure to combination antiretroviral therapy).

- **Maraviroc**

- **Dosage form**

- Tablets: 150 mg and 300 mg

- **Uses**

- CCR5-tropic HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretrovirals

- **Precautions**

- Cardiovascular disease
- Chronic hepatitis B or C
- ***Interactions:*** Appendix A
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix C
- Breast-feeding: Appendix B

- **Dose**

- **ADULT** over 18 years: 300 mg twice daily

- **Adverse effects**

- Nausea, diarrhea, abdominal pain, dyspepsia, constipation, diarrhea

- Cough
- Dizziness
- Paresthesia
- Asthenia
- Sleep disturbances
- Headache
- Weight loss
- Muscle spasms, back pain
- Taste disturbance
- Rash, pruritus
- Less commonly pancreatitis, hepatic cirrhosis, rectal bleeding, myocardial infarction, myocardial ischemia, bronchospasm, seizures, hallucinations, loss of consciousness, polyneuropathy, pancytopenia, neutropenia, lymphadenopathy, renal failure, polyuria, and myositis; osteonecrosis

6.5 ANTIPROTOZOAL MEDICINES

6.5.1 Anti-amebic and anti giardiasis medicines

Amebiasis

Amebic dysentery is caused by *Entamoeba histolytica*. It is transmitted by the feco-oral route and infection is usually caused by ingestion of cysts from contaminated food and drink. Asymptomatic carriers are common in endemic areas. In non-endemic areas, symptomless carriers should be treated with a luminal amebicide, which will reduce the risk of transmission and protect the patient from invasive amebiasis. **Diloxanide** is most widely used. Treatment with diloxanide is regarded as successful if stools are free of *E. histolytica* for 1 month. Several stool specimens should be examined when evaluating response to treatment.

Symptomatic (invasive) amebiasis may be classified as either intestinal or extra-intestinal. Intestinal forms of amebiasis include amebic dysentery and non-dysenteric

amebic colitis. Extra-intestinal amebiasis most commonly involves the liver, but in some cases may involve the skin, the genitourinary tract, the lung, and the brain. Invasive amebiasis is more likely in malnutrition, immunosuppression, and pregnancy. Amebic dysentery may take a fulminating course in late pregnancy and the puerperium period; treatment with **metronidazole** may be lifesaving. In less severe infection, metronidazole should, if possible, be avoided in the first trimester. All patients with invasive amebiasis require treatment with a systemically active compound such as **metronidazole**, or tinidazole followed by a luminal amebicide (such as diloxanide) in order to eliminate any surviving organisms in the colon. Combined preparations are useful.

In severe cases of amebic dysentery, tetracycline given in combination with a systemic amebicide lessens the risk of superinfection, intestinal perforation, and peritonitis. Hepatic abscesses should be lanced by needle aspiration.

Giardiasis

Giardiasis is caused by *Giardia intestinalis* and is acquired by oral ingestion of *Giardia* cysts. Giardiasis can be treated with tinidazole in a single dose or with another 5-nitroimidazole, such as **metronidazole**; both are highly effective and should be offered when practicable to all infected patients. Family and institutional contacts should also be treated. Larger epidemics are difficult to eradicate because of the high proportion of symptomless carriers and because excreted cysts can survive for long periods outside the human host.

Trichomoniasis

Trichomoniasis is an infection of the genitourinary tract caused by *Trichomonas vaginalis* and transmission is usually via the sexual route. In women, it can cause vaginitis, although some infected individuals remain asymptomatic. It is usually asymptomatic in men, but may cause urethritis. Patients and their sexual partners should be treated with **metronidazole** or another 5-nitroimidazole.

- **Furazolidone**

- **Dosage form**

- Tablet: 100 mg
- Oral syrup: 125 mg/5 ml

- **Uses**

- Treatment of giardiasis and cholera
- In special cases, for the treatment of other bacterial gastro-intestinal infections

- **Contraindication**

- It should not be given to infants under 1 month of age since their enzyme systems are immature (but, according to WHO recommendations, it even is not used for children under 1 year of age).

- **Precautions**

- Furazolidone should be used with caution in those with G6PD deficiency because of the risk of hemolytic anemia.
- As furazolidone is an MAOI, caution is advised for its use with other drugs, especially indirect-acting sympathomimetic amines (some sympathomimetic-acting drugs are present in anti-flu preparations; therefore it is recommended to not use them concomitantly)
- **Interactions:** Appendix A

- **Dose**

- **ADULT:** Orally in a dose of 100 mg 4 times daily
- **CHILD** and **INFANT** from 1 month of age: 1.25–1.5 mg/kg 4 times daily

Note: Usually given for 2–5 days, but may be given for up to 7 days in some patients, or for up to 7–10 days for giardiasis

- **Adverse effects**

- Gastrointestinal tract effects, including nausea and vomiting
- Dizziness, drowsiness, headache, and a general malaise also reported
- Allergic reactions, most commonly skin reactions such as rashes or angioedema, may occur.
- Hemolytic anemia may occur in patients with G6PD deficiency given furazolidone.

- **Metronidazole**

Metronidazole is a representative antibacterial and antiprotozoal agent. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 200 mg, 250 mg, 400 mg, and 500 mg
- Infusion solution: 5 mg/ml in 100 ml vial
- Oral suspension: 120 mg/5 ml and 200 mg/5 ml
- Topical cream: 0.75% in 15 g tube

- **Uses**

- Invasive amebiasis and giardiasis, trichomoniasis, anaerobic bacterial infections (Section 6.2.2)
- Eradication of *Helicobacter pylori* (Section 17)

- **Contraindication**

- See Section 6.2.2.

- **Precautions**

- See Section 6.2.2
- **Interactions:** Appendix A

- **Dose**

Invasive amebiasis, by mouth

- **ADULT** and **CHILD**: 30 mg/kg daily in 3 divided doses for 8–10 days, followed by a course of a luminal amebicide (see introductory note above)

Invasive amebiasis (if oral administration not possible), by intravenous infusion

- **ADULT** and **CHILD**: 30 mg/kg daily in 3 divided doses (until patient is able to complete course with oral drugs); subsequent course of luminal amebicide (see note above).

Giardiasis, by mouth

- **ADULT**: 2 g once daily for 3 days
- **CHILD**: 15 mg/kg daily in divided doses for 5–10 days

Urogenital trichomoniasis, by mouth

- **ADULT**: 2 g as a single dose or 400–500 mg twice daily for 7 days; sexual partners should be treated concomitantly

Note: In amebiasis and giardiasis, various dosage regimens are used and definitive recommendations should be based on local experience.

Patient advice: See Section 6.2.2.

- **Adverse effects**

- See Section 6.2.2.

6.5.2 Anti-leishmaniasis medicines

Also refer to the Leishmania Control Program of Afghanistan.

Leishmaniasis is caused by the parasitic protozoa *Leishmania* and is usually categorized as visceral, cutaneous, or mucocutaneous. It may manifest as a self-limiting, localized

skin lesion but can progress from this to mucosal involvement, to disseminated progressive disease (in the cutaneous form) or, without treatment, to a fatal disease (in the visceral form). With some exceptions, human beings are the incidental hosts of infection, and mammals, such as rodents and canids, are the reservoir hosts. The parasites are transmitted by sand flies.

Cutaneous leishmaniasis

Cutaneous leishmaniasis comprises two conditions. The “Old World” variety is caused by *L. tropica*, *L. major*, *L. infantum*, or *L. aethiopica*. The “New World” variety is caused by *L. amazonensis*, *L. mexicana*, *L. peruviana*, *L. guyanensis*, *L. panamensis*, or *L. braziliensis*. These conditions are characterized by a cell-mediated reaction of varying intensity at the site of inoculation. The New World variety tends to be more severe and slower to heal. Infections caused by *L. major*, *L. mexicana*, *L. tropica*, or *L. peruviana* are responsive to intralesional injections of antimonial compounds. Mild lesions can often be left to heal spontaneously. However, it is preferable to treat *L. tropica* infections with a view to reducing transmission since humans seem to be the only host. When the lesion is inflamed or ulcerated, larger than 3 cm in diameter, or on the face close to the eyes, there are 3 or more lesions—or when there is either obstruction of lymphatic drainage, sporotricoid forms, lesions next to joints, superinfected lesions, or destruction of cartilage that create a risk of serious disfigurement or disability—antimonials should be administered systemically.

- **Meglumine antimoniate / glucantime**

- **Dosage form**

- Injection: 30%, equivalent to 85 mg base/mL (pentavalent antimony) in 5 ml ampoule

Note: Meglumine antimoniate and sodium stibogluconate are the pentavalent antimony compound used to treat leishmaniasis.

- **Uses**

- Treatment of leishmaniasis
- **Contraindications**
 - Severe cardiac, liver, and kidney disorders
 - Breast-feeding: Appendix C
- **Precautions**
 - The risk of serious, even fatal, toxicity of pentavalent antimonials is increased in patients who concomitantly present with cardiac disease, in particular, arrhythmia; renal failure, liver disease, severe malnutrition, severely impaired general condition; advanced HIV infection; pregnancy. If one of these conditions is present, provide protein-rich diet throughout treatment and, if possible, correct iron and other nutritional deficiencies
 - Renal and hepatic impairment: Appendices D and E
 - Monitor cardiac, renal, and hepatic function
 - Treat intercurrent infection (for example, pneumonia), and if possible an alternative drug should be used
 - **Mucocutaneous disease:** Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around lesions (may be life-threatening if there is pharyngeal or tracheal involvement), which may require corticosteroid therapy.
- **Dose**

Doses are expressed in terms of pentavalent antimony.

Visceral leishmaniasis, by intramuscular injection

- **ADULT** and **CHILD:** 20 mg/kg daily for 21 days (in visceral leishmaniasis continue treatment for 28 days). Minimum dose for children weighing less than 10 kg: 2 ml (200 mg). If relapse, retreat immediately with same daily dosage.

Cutaneous leishmaniasis, by intralesional injection

- **ADULT** and **CHILD**: 1–3 ml into base of lesion once weekly for 4–8 weeks; if no apparent response, may be continued for 10–12 weeks; relapse is unusual.

Administration: Meglumine antimoniate may be given by deep intramuscular injection (if the volume of injection exceeds 10 mL, it should be divided in 2 doses: 1 in each buttock or thigh) or by slow intravenous injection (over at least 5 minutes). It may also be administered intralesionally.

- **Contraindications**

Of local therapy

- Lesion in the face close to the eyes
- 3 lesions or more
- Large lesion more than 3 cm of diameter
- Sporotricoid forms
- Lesion on the joint
- Superinfected lesions
- Children who cannot tolerate local injection

- **Adverse effects**

- Anorexia, nausea, vomiting, abdominal pain
- ECG changes (possibly requiring dose reduction or withdrawal)
- Cough
- Headache, lethargy, arthralgia, myalgia
- Raised liver enzymes
- Renal function impairment

- Rarely anaphylaxis, fever, sweating, flushing, substernal pain, vertigo, bleeding from nose or gums, jaundice, and biochemical (frequent) or clinical pancreatitis, rash
- Pain and thrombosis on intravenous administration
- Pain on intramuscular injection

- **Sodium stibogluconate**

- **Dosage form**

- Injection: Sodium stibogluconate equivalent to pentavalent antimony 100 mg/ml in 30 ml

Note: Injection should be filtered immediately before administration using a filter of 5 microns or less.

- **Use**

- Treatment of leishmaniasis

- **Precautions**

- Intravenous injections must be given slowly over 5 minutes (to reduce risk of local thrombosis) and stopped if coughing or sub-sternal pain.
- Mucocutaneous disease (*see below*)
- Monitor ECG before and during treatment
- Heart disease (withdraw if conduction disturbances occur)
- Predisposition to QT interval prolongation (including concomitant use with drugs that prolong QT interval)
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

Note: Successful treatment of mucocutaneous leishmaniasis may cause severe inflammation around the lesion (in case of inflammation of pharynx and larynx, which may be life-threatening); in these conditions, it is necessary to administer a corticosteroid.

○ **Dose**

- The dose is 20 mg/kg daily (max. 850 mg) *by intramuscular or intravenous* injection for 28 days in visceral leishmaniasis and for 20 days in cutaneous infection; the dosage varies with different geographical regions and expert advice should be obtained.
- Some early, non-inflamed lesions of cutaneous leishmaniasis can be treated with intralesional injections of sodium stibogluconate under specialist supervision.

○ **Adverse effects**

- Anorexia, nausea, vomiting, abdominal pain, diarrhea
- ECG changes
- Coughing (*see* Precautions)
- Headache, lethargy
- Arthralgia, myalgia
- Rarely jaundice, flushing, bleeding from nose or gum, sub-sternal pain (*see* Precautions), vertigo, fever, sweating, and rash
- Also reported pancreatitis and anaphylaxis
- Pain and thrombosis on intravenous administration
- Intramuscular injection also painful

6.5.3 Antimalarial medicines

Also refer to the protocols of National Malaria Program Control of Afghanistan.

Malaria, which is transmitted by anopheline mosquitoes, is caused by four species of plasmodial parasites. *Plasmodium vivax* is extensively distributed. *P. falciparum* is also widespread, and causes the most severe infections, which are responsible for nearly all malaria-related deaths. *P. ovale* is mainly confined to Africa and is less prevalent, while *P. malariae*, which causes the least severe but most persistent infections, also occurs widely.

Certain tissue forms of *P. vivax* and *P. ovale*, which persist in the liver for many months and even years, are responsible for relapses. Such latent forms are not generated by *P. falciparum* or *P. malariae*. Recrudescence of these infections results from persistent blood forms in inadequately treated or untreated patients.

6.5.3.1 For curative treatment

Blood schizontocides, which suppress malaria by destroying the asexual blood forms of the parasites, are the mainstay of the treatment of acute malaria; some are used for prophylaxis. They include the 4-aminoquinolines (**amodiaquine** [not in LML *Afghanistan*] and **chloroquine**), the related arylaminoalcohols (**mefloquine** [not in LML *Afghanistan*] and **quinine**), and artemisinin and its derivatives (**artemether** and **artesunate**). Blood schizontocides are not active against intrahepatic forms and therefore they do not eliminate infections caused by *P. vivax* and *P. ovale*.

Combinations of some antimetabolites act synergistically. For example, a combination of **pyrimethamine + sulfadoxine** is an effective blood schizontocide; on their own, these substances are of little value because they act only slowly. Some antibiotics (for example, the tetracyclines, and **doxycycline**, in particular) are blood schizontocides; the tetracyclines are used primarily as adjuncts to quinine where multidrug-resistant *P. falciparum* is prevalent.

Treatment of falciparum malaria

To reduce the risk of *P. falciparum* resistance, 2 or more blood schizontocides with different mechanisms of action should be used in combination to treat falciparum malaria (one of which should be an artemisinin derivative). The following artemisinin-based combinations are recommended for the treatment of uncomplicated falciparum malaria:

artemether + lumefantrine (*not in LML Afghanistan*)

artesunate + amodiaquine (*not in LML Afghanistan*)

artesunate + mefloquine (*not in LML Afghanistan*)

artesunate + sulfadoxine + pyrimethamine

Pregnancy and breast-feeding. In the first trimester of pregnancy, quinine in combination with clindamycin for 7 days is the treatment of choice; this combination can be used throughout pregnancy. If clindamycin is not available, quinine should be given as monotherapy. In the second and third trimesters, an artemisinin-based combination therapy or artesunate and clindamycin can be given for 7 days. Breast-feeding women should receive standard antimalarial treatment (including artemisinin-based combination therapy), but not regimens that include tetracyclines or dapsone.

Treatment of severe cases. Treatment of *severe* falciparum malaria requires either parenteral artemether or artesunate, or parenteral quinine. Intravenous artesunate is the drug of choice in low-to-moderate transmission areas, or outside malaria endemic areas. Parenteral antimalarials are also used to initiate treatment in patients unable to take oral treatment. The risk of death in severe malaria is greatest in the first 24 hours; it is therefore recommended that the first dose of parenteral treatment be given before referral to a health facility.

Combination antimalarial treatment should start as soon as patients are able to take oral medication. Fever and vomiting associated with acute malaria should be treated with an antipyretic (for example, paracetamol) and an anti-emetic as appropriate.

HIV infection

Patients with HIV infection who develop malaria should receive standard antimalarial treatment regimens. The use of sulfadoxine + pyrimethamine should be avoided in HIV-infected patients receiving sulfamethoxazole with trimethoprim for prophylaxis against opportunistic infection with *Pneumocystis carinii* (see Section 6.5.4) because of the increased risk of adverse reactions to sulfonamides.

Benign malarias

Chloroquine is the drug of choice for *P. vivax* infection; **primaquine** is added for a radical cure (to destroy parasites in the liver and thus prevent relapses). Alternatives in chloroquine-resistant areas include amodiaquine or an artemisinin derivative or mefloquine, in all cases followed by primaquine for radical cure. Severe or complicated vivax malaria is treated as severe falciparum malaria.

Malaria caused by infection with *P. ovale* or *P. malariae* is generally treated with chloroquine. For radical cure of *P. ovale*, primaquine is added as for vivax malaria.

Pregnancy. In pregnant patients with *P. vivax* or *P. ovale* infection, radical cure with primaquine should be postponed until after delivery; chloroquine at a dose of 600 mg (as the base) weekly can be given until then.

Malaria epidemics

In malaria epidemics, artemisinin-based combinations are the recommended treatment. For chloroquine-sensitive *P. vivax* epidemics, the recommended treatment is chloroquine (25 mg/kg divided over 3 days) in combination with primaquine (250 micrograms/kg daily for 14 days). When artemisinin-based combinations are not available

during epidemics, the most effective alternative should be used until they become available.

Pregnancy. For severe malaria in pregnancy during an epidemic, intravenous artesunate is the treatment of choice; the preferred alternative is intramuscular artemether.

Chloroquine, a rapidly acting schizontocide, is well tolerated, safe, and inexpensive. It can be used to treat malaria wherever the parasites remain susceptible. However, widespread resistance has limited its value in the treatment of falciparum malaria. Chloroquine-resistant strains of *P. vivax* have been reported in parts of Oceania, Indonesia, East Timor, and Peru. *P. malariae* and *P. ovale* remain fully sensitive to chloroquine.

The combination of **sulfadoxine + pyrimethamine** is also used in combination with other antimalarials for the treatment of uncomplicated *P. falciparum* infection. Resistance to sulfadoxine + pyrimethamine is now widespread, particularly in southeast Asia and South America, and to a lesser extent in east and central Africa. Because sulfonamides are associated with hemolysis and methemoglobinemia in neonates, quinine is preferred for chloroquine-resistant malaria during pregnancy.

Quinine, given orally, is used in combination with clindamycin or doxycycline to treat relapses of *P. falciparum* infections that occur within 14 days of treatment and are likely to be unresponsive to other drugs. Resistance to quinine was, until recently, rare, but the prevalence of resistant strains is now increasing in parts of southeast Asia and South America. Doxycycline, which is an effective oral blood schizontocide, is given with quinine, except in pregnant women and children under 8 years.

Preparations of artemisinin or its derivatives (**artemether** or **artesunate**) are used in combination with other antimalarial drugs for the treatment of falciparum malaria. When given alone or in combination with other rapidly eliminated antimalarials, a 7-day course is required, but when given in combination with slowly eliminated antimalarials, a 3-day

course is effective. They should not be used in the first trimester of pregnancy, except where no other effective antimalarial medicine is available. Parenteral artemether or artesunate is an effective alternative to quinine for the treatment of severe falciparum malaria and are preferred in areas with decreased efficacy of quinine.

A fixed-dose oral formulation of artemether + lumefantrine is available for the treatment of uncomplicated falciparum malaria; the combination is not for use in the first trimester of pregnancy. Oral multidrug therapy in blister packs is available for artesunate and amodiaquine, artesunate and mefloquine, and artesunate and sulfadoxine + pyrimethamine.

- **Artemether**

- **Dosage form**

- Oily injection: 20 mg/ml, 40 mg/ml, and 80 mg/ml in 1 ml ampoule

- **Uses**

- Treatment of severe *P. falciparum* malaria in health centers (*see also* introductory note above). *For further information, refer to Protocols of Malaria and Leishmaniasis National Program Control in Afghanistan.*

- **Contraindications**

- First trimester of pregnancy: Appendix B

- **Precautions**

- **Skilled tasks:** Dizziness may impair ability to perform skilled tasks (for example, operating machinery or driving).

- **Dose**

- Treatment of severe P. falciparum malaria (in health centers), by intramuscular injection*

- **ADULT** and **CHILD** over 6 months: Loading dose of 3.2 mg/kg on day 1, then 1.6 mg/kg daily until patient can tolerate oral medication, or up to a maximum of 7 days; or at least 2 days after treatment with artemether, complete doses of artesunate + sulfadoxine-pyrimethamine should be given *by mouth*
- All pregnant women with malaria should be referred to hospital.

Administration: Since small volumes are required for children, a 1 ml syringe should be used to ensure correct dosage.

- **Adverse effects**

- Headache, nausea, vomiting, abdominal pain, diarrhea
- Dizziness, tinnitus, neutropenia, elevated liver enzyme values
- Cardiotoxicity (after high doses)
- Neurotoxicity (in animal studies)

- **Artesunate**

- **Dosage form**

- Tablets: 50 mg, 100 mg, 300 mg, and 600 mg in combination with sulfadoxine + pyrimethamine

- **Uses**

- Treatment of uncomplicated malaria caused by *P. falciparum* in combination with other antimalarials

- **Contraindications**

- First trimester of pregnancy: Appendix B

- **Precautions**

- Risk of recurrence if used alone in non-immune patients

- **Skilled tasks:** Dizziness may impair ability to perform skilled tasks (for example, operating machinery or driving).

- **Dose**

Treatment of uncomplicated falciparum malaria (in combination with other antimalarial medicines) by mouth

- **ADULT** and **CHILD** over 5 months: 4 mg/kg daily for 3 days

- **Adverse effects**

- Headache, nausea, vomiting, abdominal pain, diarrhea, dizziness, tinnitus, neutropenia, elevated liver enzyme values
- ECG abnormalities including prolongation of the QT interval
- Temporary suppression of reticulocyte response and induction of blackwater fever, reported
- Neurotoxicity (in animal studies)

- **Chloroquine**

- **Dosage form**

- Tablet: 150 mg (base)
- Oral liquid: 50 mg/5 ml (base)
- Tablets: 100 mg and 150 mg (hydroxychloroquine)

Note: Chloroquine base 150 mg is equivalent to chloroquine sulfate 200 mg or chloroquine phosphate 250 mg.

- **Uses**

- Treatment of acute malaria caused by *P. malariae*, *P. vivax*, and *P. ovale* (followed in *P. vivax* and *P. ovale* infections by primaquine to eliminate intrahepatic forms; *see also* introductory note above)
- Prophylaxis of malaria (*see* Section 6.5.3.2)

- Rheumatic disorders (Section 2.4)
- **Precautions**
 - If patient continues to deteriorate after chloroquine, suspect resistance and administer quinine intravenously as emergency measure.
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Pregnancy (but in acute malaria, benefit is usually considered to outweigh risk): Appendix B
 - Breast-feeding: Appendix C
 - May exacerbate psoriasis
 - Neurological disorders (if history of epilepsy do not use for prophylaxis)
 - May aggravate myasthenia gravis
 - Severe gastrointestinal disorders
 - G6PD deficiency
 - Avoid concurrent therapy with hepatotoxic drugs
 - **Interactions:** Appendix A
- **Dose**

Note: All doses are in terms of chloroquine base.

Treatment of acute malaria, by mouth

- **ADULT and CHILD:** 10 mg/kg followed by 5 mg/kg 6–8 hours later on day 1, then 5 mg/kg daily on day 2 and day 3, or 10 mg/kg for day 1 and day 2, followed by 5 mg/kg daily on day 3 (total dose, 25 mg/kg over 3 days)

Patient advice: Oral chloroquine should be taken after meals to minimize nausea and vomiting; if part or all of a dose is vomited, the same amount must be re-administered immediately.

- **Adverse effects**

- Headache, gastrointestinal disturbances
- Also convulsions
- Visual disturbances (retinopathy associated with long-term, high-dose therapy or inappropriate self-medication)
- Depigmentation or loss of hair
- Rash
- Pruritus (may become intolerable)
- Bone marrow suppression
- Hypersensitivity reactions including urticaria and angioedema
- Atrioventricular block (may be result of inappropriate self-medication)
- Porphyria and psoriasis in susceptible individuals

- **Doxycycline**

Doxycycline is a complementary list medicine for the treatment of malaria.

- **Dosage form**

- Capsule: 100 mg (as hydrochloride)

- **Uses**

- Supplement to quinine or artesunate treatment for multidrug-resistant *P. falciparum* malaria
- Short-term prophylaxis of multidrug-resistant *P. falciparum* malaria (Section 6.5.3.1)
- Bacterial infections (Section 6.2.2)
- Moderate acne (Section 13.5)

- **Contraindications**

- Pregnancy: Appendix B
- Children under 8 years

- Porphyria
- Systemic lupus erythematosus

- **Precautions**

- Avoid exposure to sunlight or sunlamps (risk of photosensitivity reactions; *see* Adverse effects)
- Renal impairment: Appendix D
- Hepatic impairment: Appendix E
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Dose**

Supplement to quinine or artesunate treatment for multidrug-resistant P. falciparum malaria, by mouth

- **ADULT** and **CHILD** over 8 years: 100 mg twice daily for 7–10 days

Patient advice: Capsules should be swallowed whole with plenty of fluid while sitting or standing to prevent esophageal irritation. May be given with food or milk to counter gastric irritation.

- **Adverse effects**

- *See* Section 6.5.3.2.

- **Primaquine**

- **Dosage form**

- Tablets: 7.5 mg and 15 mg (as diphosphate)

- **Uses**

- Elimination of intrahepatic forms of *P. vivax* and *P. ovale* (after standard chloroquine therapy)

- Elimination of gametocytes of *P. falciparum* (after standard therapy with a blood schizontocide)
- **Contraindications**
 - Pregnancy (treatment with primaquine should be delayed until after delivery): Appendix B
 - Breast-feeding: Appendix C
 - Conditions that predispose to granulocytopenia (including active rheumatoid arthritis and lupus erythematosus)
- **Precautions**
 - Monitor blood count (if either methemoglobinaemia or hemolysis occurs, withdraw treatment and consult a physician)
 - G6PD deficiency (exclude before radical treatment for *P. vivax* and *P. ovale* malaria; however, this is not necessary before single-dose gametocytocidal treatment)
 - **Interactions:** Appendix A
- **Dose**

Note: All doses are in terms of primaquine base.

Radical treatment of P. vivax and P. ovale malaria (after standard chloroquine therapy), by mouth

- **ADULT:** 250 micrograms/kg daily (or 15 mg daily) for 14 days
- **CHILD:** 250 micrograms/kg daily for 14 days

In G6PD deficiency

- **ADULT:** 750 micrograms/kg once a week for 8 weeks
- **CHILD:** 500–750 micrograms/kg once a week for 8 weeks

Gametocytocidal treatment of P. falciparum malaria (after standard blood schizontocide therapy), by mouth

- **ADULT** and **CHILD**: 250 micrograms/kg as a single dose

- **Adverse effects**

- Anorexia, nausea and vomiting, abdominal pain
- Acute hemolytic anemia (frequently in G6PD deficiency)
- Rarely methemoglobinemia, hemoglobinuria, agranulocytosis, granulocytopenia, and leukopenia

- **Quinine**

- **Dosage form**

- Injection: 300 mg (quinine dihydrochloride)/mL in 2 ml ampoule
- Tablet: 300 mg (quinine sulfate)

- **Uses**

- Treatment of multidrug-resistant *P. falciparum* malaria, alone or in combination with other antimalarial drugs

- **Contraindications**

- Hemoglobinuria
- Optic neuritis
- Tinnitus
- Myasthenia gravis

- **Precautions**

- Atrial fibrillation, conduction defects, or heart block (monitor for signs of cardiac toxicity and blood glucose and electrolyte concentrations during intravenous use)
- Pregnancy (but in acute malaria benefit is usually considered to outweigh risk): Appendix B

- Breast-feeding: Appendix C
- Renal impairment: Appendix D
- G6PD deficiency
- **Interactions:** Appendix A

○ **Dose**

Note: 100 mg of quinine (anhydrous base) or 169 mg quinine bisulfate or 122 mg quinine dihydrochloride or 121 mg quinine sulfate

Treatment of multidrug-resistant P. falciparum malaria, by mouth

- **ADULT:** 10 mg/kg (quinine sulfate) every 8 hours for 7 days

Patient advice: If all or part of a dose is vomited within 1 hour of administration, the same amount must be re-administered immediately.

Treatment of multidrug-resistant P. falciparum malaria (in patients unable to take quinine by mouth), by slow intravenous infusion (over 4 hours)

- **ADULT:** Initially 20 mg/kg (quinine dihydrochloride), followed by 10 mg/kg (quinine dihydrochloride) every 8 hours
- **CHILD:** Initially 20 mg/kg (quinine dihydrochloride), followed by 10 mg/kg (quinine dihydrochloride) every 12 hours
- Initial dose should be halved in patients who have received quinine, quinidine, or mefloquine during the previous 12–24 hours

Treatment of multidrug-resistant P. falciparum malaria (when patient is able to take the drug by mouth)

- The complete course of artesunate (4 mg/kg daily) with sulfadoxine + pyrimethamine (25 mg/kg for sulfadoxine), or continue quinine by mouth (10 mg/kg 3 times a day) with doxycycline (3.5 mg/kg daily) or clindamycin (10 mg/kg twice daily) should be given for 7 days

Caution: Do not use doxycycline in pregnant women or children younger than 8 years.

Dilution and administration: According to manufacturer's directions; intravenous injection of quinine is so hazardous that it has been superseded by infusion; where facilities for intravenous infusion are unavailable, an appropriate dilution may be administered by intramuscular injection.

- **Adverse effects**

- Cinchonism (tinnitus, headache, blurred vision, temporary blindness, altered auditory acuity, nausea, diarrhea, hot and flushed skin, rash, and confusion)
- Hypersensitivity reactions including angioedema
- Rarely hemorrhage and asthma
- Hypoglycemia (especially after parenteral administration)
- Renal damage (culminating in acute renal failure and anuria)
- Blood disorders
- Cardiovascular, gastrointestinal, and central nervous system effects
- Very toxic in overdosage (immediate medical attention required)

- **Sulfadoxine + pyrimethamine**

- **Dosage form**

- Tablets: 500 mg + 25 mg; 1,000 mg + 50 mg; 1,500 mg + 75 mg

Note: The co-blister dosage forms include artesunate, respectively, 50 and 100 mg; 300 mg; and 600 mg.

- **Uses**

- Treatment of falciparum malaria in combination with other antimalarials (*see also* introductory note above)

- **Contraindications**

- Hypersensitivity to sulfonamides or pyrimethamine
- Severe hepatic or renal impairment (except where no alternative treatments available)

- **Precautions**

- Blood disorders (avoid unless specialist supervision is available and discontinue immediately if blood disorder occurs)
- Rash, sore throat, mouth ulcers, or shortness of breath (withdraw treatment)
- G6PD deficiency
- Predisposition to folate deficiency
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Dose**

Treatment of uncomplicated P. falciparum malaria (in combination with other antimalarials; see introductory note above), by mouth

- **ADULT:** Sulfadoxine 1.5 g + pyrimethamine 75 mg (3 tablets of 500 mg + 25 mg) as a single dose
- **CHILD** 5–10 kg: 250 mg + 12.5 mg (or ½ tablet of 500 mg + 25 mg)
- **CHILD** 11–20 kg: 1 tablet of 500 mg + 25 mg
- **CHILD** 21–30 kg: 1½ tablets of 500 mg + 25 mg
- **CHILD** 31–45 kg: 2 tablets of 500 mg + 25 mg, as a single dose

Note: For the treatment of uncomplicated *P. falciparum* malaria, in order to prevent monotherapy, the co-blister form should be administered. Sulfadoxine 25 mg/kg, pyrimethamine 1.25 mg/kg, and artesunate 4 mg/kg, daily for 3

days. It can be used in the second and third trimesters of pregnancy. As the progression of disease in pregnant women may be rapid, they should be treated urgently. The initial dose should be given to the patient under direct supervision and patient should be monitored for half an hour. If the patient vomits during first half an hour, the same amount should be administered immediately. If vomiting persists, the patient needs to be hospitalized.

○ **Adverse effects**

- Rash, pruritus, slight hair loss
- Rarely erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis
- Gastrointestinal disturbances including nausea, vomiting, and stomatitis
- Rarely hepatitis, leukopenia, thrombocytopenia, megaloblastic anemia, and purpura (withdraw treatment)
- Fatigue, headache, fever, and polyneuritis also reported
- Pulmonary infiltrates such as eosinophilic or allergic alveolitis resulting in cough or shortness of breath (withdraw treatment)

6.5.3.2 For prophylaxis

No drug regimen gives assured protection to everybody, and indiscriminate use of antimalarials can increase the risk of inducing resistance. Avoidance of mosquito bites using insect repellents, mosquito nets (preferably impregnated with an insecticide), and door and window screens are important preventive strategies.

Chloroquine, which is usually well tolerated at the required dosage for prophylaxis, is preferred where *P. falciparum* remains fully sensitive. Chloroquine is best started 1 week before exposure, and continued for at least 4 weeks after the last exposure in non-immune individuals. This is sufficient to ensure elimination of *P. falciparum* and *P. malariae*, but not of *P. vivax* and *P. ovale*, whose residual hepatic forms survive. Chloroquine can be used during pregnancy.

Doxycycline is an alternative in areas of high risk or where multidrug resistance has been reported; it should not be given during pregnancy.

- **Chloroquine**

- **Dosage form**

- Tablet: 150 mg (base)
 - Oral liquid: 50 mg/5 ml (base)
 - Tablets: 100 mg and 150 mg (hydroxychloroquine)

Note: Chloroquine base 150 mg is equivalent to chloroquine sulfate 200 mg or chloroquine phosphate 250 mg.

- **Uses**

- Prophylaxis of malaria
 - In non-immune individuals at risk alone of acute malaria caused by *P. malaria*, *P. vivax*, *P. ovale* (see Chloroquine, Section 6.5.3.1)
 - Rheumatic disorders (Section 2.4)

- **Precautions**

- See Chloroquine, Section 6.5.3.1.
 - **Interactions:** Appendix A

- **Dose**

Prophylaxis of malaria, by mouth

- **ADULT:** 300 mg once a week
 - **CHILD:** 5 mg/kg once a week during the stay in malarious areas
 - Chloroquine is best started 1 week before exposure, and continued for at least 4 weeks after the last exposure in non-immune individuals.

Patient advice: Inform travelers about the importance of taking measures to avoid mosquito bites, of taking prophylaxis regularly, and of the need to visit a doctor immediately if they fall ill within 1 year, and especially within 3 months, of their return from a malaria-endemic area.

Dilution and administration: According to manufacturer's directions. Avoid rapid parenteral administration (risk of toxic plasma concentrations and fatal cardiovascular collapse).

- **Adverse effects**
 - See Chloroquine, Section 6.5.3.1.

- **Doxycycline**

- **Dosage form**
 - Capsule: 100 mg (as hydrochloride)
- **Uses**
 - Short-term prophylaxis of multidrug-resistant *P. falciparum* malaria
 - Bacterial infections (Section 6.2.2)
 - Moderate acne (Section 13.5)
- **Contraindications**
 - Pregnancy: Appendix B
 - Children under 8 years
 - Porphyria
 - Systemic lupus erythematosus
- **Precautions**
 - Avoid exposure to sunlight or sunlamps (risk of photosensitivity reactions; see Adverse effects)
 - Renal impairment: Appendix D

- Hepatic impairment: Appendix E
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

○ **Dose**

Short-term prophylaxis of malaria, by mouth

- **ADULT:** 100 mg daily for up to 8 weeks
- **CHILD** over 8 years: 1.5 mg/kg 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.
- **Caution:** Not for pregnant women or children under 8 years old

Patient advice: Capsules should be swallowed whole with plenty of fluid while sitting or standing to prevent esophageal irritation. May be given with food or milk to counter gastric irritation.

○ **Adverse effects**

- Gastrointestinal disturbances
- Anorexia
- Flushing, tinnitus
- Photosensitivity reactions
- Hypersensitivity reactions
- Headache and visual disturbances
- Hepatotoxicity, blood disorders, pancreatitis, and antibiotic-associated colitis reported
- Staining of growing teeth and occasional dental hypoplasia

6.5.4 Anti-pneumocystosis and anti-toxoplasmosis medicines

Pneumocystosis

Pneumocystis carinii (*Pneumocystis jiroveci*) is classified as a protozoan although there is some evidence to suggest that it is a fungus. *P. carinii* (*P. jiroveci*) pneumonia is probably acquired by the airborne route. In otherwise healthy persons, it rarely produces signs of infection. However, it is a frequent cause of opportunistic infection in immunosuppressed, debilitated, or malnourished patients; it is the commonest cause of pneumonia in AIDS and the most frequent immediate cause of death in these patients.

Sulfamethoxazole + trimethoprim is the treatment of choice for *P. carinii* (*P. jiroveci*) pneumonia; it is also used for prophylaxis in high-risk patients. Pentamidine (not in *LML Afghanistan*) is used in patients unresponsive to, or intolerant of, sulfamethoxazole + trimethoprim.

The treatment of *P. carinii* (*P. jiroveci*) infections must only be undertaken with specialist supervision, and where there are appropriate monitoring facilities.

Toxoplasmosis

Toxoplasmosis is caused by infection with the protozoan parasite *Toxoplasma gondii*. Most infections are self-limiting and do not require treatment. However, in immunodeficiency, primary infection may result in encephalitis, myocarditis, or pneumonitis; impairment of immunity (such as that which occurs in AIDS) in a previously infected person may result in encephalitis or meningo-encephalitis. Congenital transmission may occur if there is a primary infection in early pregnancy or if the mother is immunodeficient. Such cases often result in spontaneous abortion, fetal death, or severe congenital disease. Spiramycin can reduce transmission of maternal infection to the fetus. Ocular toxoplasmosis causes chorioretinitis and is often the result of a childhood infection that only becomes apparent in adulthood.

The treatment of choice for toxoplasmosis is a combination of **pyrimethamine** and sulfadiazine; a folate supplement is also given to counteract the megaloblastic anemia associated with these drugs.

- **Pyrimethamine**

- **Dosage form**

- Tablet: 25 mg

- **Uses**

- Toxoplasmosis (with sulfadiazine)
 - Malaria (with sulfadoxine + artesunate; see Section 6.5.3.1)

- **Contraindications**

- Hepatic and renal impairment

- **Precautions**

- Pregnancy (avoid in first trimester but can be given in later pregnancy if danger of congenital transmission): Appendix B
 - Breast-feeding: Appendix C
 - Blood counts required with prolonged treatment
 - Give folate supplements throughout treatment
 - **Interactions:** Appendix A

- **Dose**

Prevention of congenital transmission of toxoplasmosis (in second and third trimesters of pregnancy), by mouth

- **ADULT:** 25 mg daily for 3–4 weeks

Treatment of toxoplasmosis in neonates, by mouth

- **NEONATE:** 1 mg/kg daily; if neonate has overt disease, continue treatment for 6 months; if neonate is without overt disease but was born to a mother infected during pregnancy, treat for 4 weeks, followed by further courses if infection is confirmed.

Treatment of toxoplasmosis in immunodeficiency, by mouth

- **ADULT:** 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, by mouth

- **ADULT:** 75 mg daily for 3 days, then 25 mg daily for 4 weeks; in unresponsive patients, 50 mg daily for a further 4 weeks

Note: For the treatment of toxoplasmosis, pyrimethamine must always be taken with sulfadiazine.

- **Adverse effects**

- Depression of hematopoiesis with high doses
- Megaloblastic anemia
- Rash
- Insomnia
- Gastrointestinal disturbances

- **Sulfamethoxazole + trimethoprim**

- **Dosage form**

- Tablets: 100 mg + 20 mg, 400 mg + 80 mg, 800 mg + 160 mg
- Oral suspension: 200 mg + 40 mg per 5 ml or 400 mg + 80 mg per 5 ml

- **Uses**

- *Pneumocystis carinii* (*Pneumocystis jiroveci*) pneumonia

- Bacterial infections (Section 6.2.2)
- **Contraindications**
 - Hypersensitivity to sulfonamides or trimethoprim
 - Porphyria

- **Precautions**
 - See Section 6.2.2.

- **Dose**

Treatment of P. carinii (P. jiroveci) pneumonia, by mouth or by intravenous infusion

- **ADULT** and **CHILD**: Sulfamethoxazole, up to 100 mg/kg daily + trimethoprim, up to 20 mg/kg daily in 2–4 divided doses for 14–21 days

Prophylaxis of P. carinii (P. jiroveci) pneumonia, by mouth

- **ADULT** and **CHILD**: Sulfamethoxazole, 25 mg/kg + trimethoprim, 5 mg/kg in 2 divided doses on alternate days (3 times a week)

Dilution and administration: According to manufacturer's directions

- **Adverse effects**
 - See Section 6.2.2.

SECTION 7: Antimigraine medicines

Chronic recurrent headache is associated with many disorders, both somatic and psychogenic. Consequently, accurate diagnosis must be made before appropriate treatment can be initiated for migraine. Untreated, migraine attacks last for several hours and sometimes as long as 3 days.

Migraine headache is frequently accompanied by gastrointestinal disturbance, including nausea and vomiting. The headache may be preceded or accompanied by aura (classical migraine), which is characterized by visual disturbances such as flickering lines and fragmented vision or sensory disturbances such as tingling or numbness; rarely hemiparesis or impaired consciousness may occur. Migraine without aura (common migraine) is the more common form, occurring in about 75% of patients who experience migraine.

Emotional or physical stress, lack of or excess sleep, missed meals, menstruation, alcohol, and specific foods (including cheese and chocolate) are often identified as precipitating factors; oral contraceptives may increase the frequency of attacks. Avoidance of precipitating factors can prevent or reduce the frequency of attacks. Women taking combined oral contraceptives who experience an onset or increase in frequency of headaches should be advised of other contraceptive measures.

The two principal strategies of migraine management are treatment of acute attacks and prevention of attacks (prophylaxis).

LML strengths and dosage forms are marked in *italic* with an asterisk.

7.1 FOR TREATMENT OF ACUTE ATTACKS

Treatment of acute attacks may be non-specific using simple analgesics; if nausea and vomiting are features of the attack, an anti-emetic drug may be given. Treatment is generally by mouth; some drugs are available as suppositories, which may be used if the

oral route is either not effective (oral bioavailability is poor, or absorption from the gut is impaired by vomiting), or not practicable (patient is unable to take drugs orally).

Excessive use of antimigraine medication, which includes analgesics, 5HT₁ agonists, and ergotamine, is associated with medication-overuse headache (analgesic-induced headache); therefore, increasing consumption of these medicines requires careful management.

Simple analgesics can be effective in mild-to-moderate forms of migraine if taken early in the attack; most migraine headaches respond to paracetamol (acetaminophen), acetylsalicylic acid (aspirin), or other non-steroidal anti-inflammatory medicines (NSAIDs), such as ibuprofen. Peristalsis is often reduced during migraine attacks and, if available, a dispersible or effervescent preparation of the drug is preferred because of enhanced absorption compared with a conventional tablet. The risk of Reye syndrome due to acetylsalicylic acid in children under 16 years can be avoided by giving paracetamol instead.

An anti-emetic, such as metoclopramide, given as a single dose of 10–20 mg orally or by intramuscular injection at the onset of a migraine attack, preferably 10–15 minutes before the analgesic, is useful not only in relieving nausea but also in restoring gastric motility, thus improving absorption of the analgesic. Specific antimigraine drugs, such as the 5HT₁ agonist sumatriptan, are used when analgesics are ineffective; they act on the 5HT (serotonin) 1B/1D receptors and can be used during the established headache phase of an attack.

Ergot alkaloids should no longer be used in the treatment of migraine; they are associated with many side effects and must be avoided in cerebrovascular or cardiovascular disease. Products that contain barbiturates or codeine are also undesirable since they may cause physical dependence and withdrawal headaches.

- **Acetylsalicylic acid**

Also known as aspirin

- **Dosage form**

- Tablets: 75 mg, 100 mg, 300 mg, 325 mg, and 500 mg

- **Uses**

- Acute migraine attacks
- Tension headache
- Pyrexia, mild-to-moderate pain, and inflammation (Section 2.1)
- Antiplatelet (Section 12.5)

- **Contraindications**

- Hypersensitivity (including asthma, angioedema, urticaria, or rhinitis) to acetylsalicylic acid or any other NSAID
- Children and adolescents under 16 years (risk of Reye syndrome)
- Previous or active peptic ulceration
- Hemophilia and other bleeding disorders
- Not for treatment of gout

- **Precautions**

- Asthma, allergic disease
- Renal impairment: Appendix D
- Hepatic impairment: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Elderly
- G6PD-deficiency
- Dehydration
- **Interactions:** Appendix A

- **Dose**

Treatment of acute migraine attack, by mouth preferably with or after food

- **ADULT:** 300–900 mg at first sign of attack, repeated every 4–6 hours if necessary; maximum 4 g daily
- **CHILD** under 16 years: Not recommended

- **Adverse effects**

- See Section 2.1.

- **Ergotamine**

- **Dosage form**

- Tablet: 1 mg (as tartrate)

- **Uses**

- Treatment of acute migraine and migraine variants unresponsive to analgesics

- **Contraindications**

- Peripheral vascular disease, coronary heart disease, obliterative vascular disease, and Raynaud's syndrome
- Temporal arteritis, sepsis, severe or inadequately controlled hypertension
- Hyperthyroidism
- Acute porphyria

- **Precautions**

- Risk of peripheral vasospasm
- Elderly
- Dependence
- Cardiac disease

- Anemia
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - ***Interactions:*** Appendix A
- **Dose**
- **ADULT:** 1 tablet at onset followed after 30 minutes by 0.5–1 tablet if required; repeated after 30 minutes if needed; maximum 3 tablets in 24 hours, maximum 6 tablets in 1 week
 - Not recommended for children
- **Adverse effects**
- Abdominal pain, nausea, vomiting
 - Dizziness
 - Less commonly diarrhea, pain, and weakness in extremities, cyanosis, peripheral vasoconstriction, paresthesia, and hypoesthesia
 - Rarely intestinal ischemia, arrhythmias, increased blood pressure, bradycardia, tachycardia, dyspnea, ergotism (including absence of pulse and numbness in extremities), myalgia, rash, and urticaria
 - Very rarely myocardial ischemia, myocardial infarction, heart-valve fibrosis, and gangrene
 - Constipation, dry mouth cerebral ischemia, thrombosis, drowsiness, sleep disturbances, tremor, seizures, extrapyramidal effects, anxiety, depression, confusion, hallucinations, renal artery spasm, urinary retention, blood disorders, blurred vision, and arthralgia also reported

- **Paracetamol**

Also known as acetaminophen

- **Dosage form**

- Oral liquid: 120 mg/5 ml and 250 mg/5 ml
- Tablets: 100 mg, 325 mg, and 500 mg
- Oral ingestion drop: 100 mg/ml
- Suppository, rectal: 125 mg
- Infusion solution: 10 mg/ml in 100 ml vial
- Injection: 225 mg/3 ml

- **Uses**

- Acute migraine attacks, tension headache
- Mild-to-moderate pain
- Pyrexia (Section 2.1)

- **Precautions**

- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Alcohol dependence
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Overdosage: Section 4.2.
- **Interactions:** Appendix A

- **Dose**

Treatment of acute migraine attack, by mouth

- **ADULT:** 0.5–1 g at first sign of attack, repeated every 4–6 hours if necessary, maximum 4 g daily

- **CHILD** 6–12 years: 250–500 mg at first sign of attack, repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours

Treatment of acute migraine attack, by rectum

- **ADULT** and **CHILD** over 12 years: 0.5–1 g at first sign of attack, repeated every 4–6 hours if necessary, maximum, 4 doses in 24 hours
- **CHILD** 6–12 years: 250–500 mg at first sign of attack, repeated every 4–6 hours if necessary, maximum 4 doses in 24 hours

- **Adverse effects**

- Rare, but rashes and blood disorders (including thrombocytopenia, leukopenia, and neutropenia) reported
- **Important:** Liver damage (and less frequently renal damage) following overdosage

7.2 FOR PROPHYLAXIS

Prophylactic treatment for migraine should be considered for patients in whom:

- Treatment of acute migraine attacks is ineffective or not possible
- The frequency of migraine attacks is increasing
- Migraine attacks occur more than once or twice a month
- The severity or duration of migraine attacks is disabling

Prophylaxis can reduce the severity and frequency of attacks but does not eliminate them completely; additional symptomatic treatment is still needed. However, long-term prophylaxis is undesirable and treatment should be reviewed at 6-monthly intervals.

Of the many drugs that have been advocated for migraine prophylaxis, beta-adrenoceptor antagonists (beta-blockers) are most frequently used. **Propranolol**, a non-selective beta-blocker, and other related compounds with a similar profile, such as atenolol, are

generally preferred. Tricyclic antidepressants, including amitriptyline or calcium-channel-blocking drugs such as verapamil may be of value.

- **Propranolol**

Propranolol is a representative beta-adrenoceptor antagonist. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 10 mg, 20 mg, and 40 mg

- **Uses**

- Prophylaxis of migraine
- Angina, cardiac arrhythmia, hypertension, anxiety, prophylaxis for myocardial infarction, pheochromocytoma (only with an alpha-blocker).
See Section 12.1.

- **Contraindications**

- Asthma or history of obstructive airway disease, uncontrolled heart failure, Prinzmetal angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree atrioventricular block, cardiogenic shock, metabolic acidosis, or severe peripheral arterial disease
- Pheochromocytoma (unless used with an alpha-blocker)

- **Precautions**

- First-degree atrioventricular block
- Renal impairment: Appendix D
- Liver disease: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Portal hypertension

- Diabetes mellitus
- Myasthenia gravis
- History of hypersensitivity (increased reaction to allergens and reduced response to epinephrine [adrenaline])
- **Interactions:** Appendix A

○ **Dose**

Prophylaxis of migraine, by mouth

- **ADULT:** Initially 40 mg 2–3 times daily, increased by same amount at weekly intervals if necessary; usual maintenance dose is in the range of 80–160 mg daily
- **CHILD** under 12 years: 20 mg 2–3 times daily

Note: Excessive bradycardia can be countered with intravenous injection of atropine sulfate 0.6–2.4 mg in divided doses of 600 micrograms.

○ **Adverse effects**

- Bradycardia, heart failure, hypotension, conduction disorders, bronchospasm, peripheral vasoconstriction, exacerbation of intermittent claudication, and Raynaud's phenomenon
- Gastrointestinal disturbances, fatigue, and sleep disturbances, including nightmares
- Rarely rash, dry eyes (reversible), sexual dysfunction, and exacerbation of psoriasis

● **Metoprolol**

○ **Dosage form**

- Tablets: 50 mg and 100 mg

○ **Uses**

- Prophylaxis of migraine, hypertension (Section 12.3), angina (Section 12.1), arrhythmia, arrhythmia during surgery, and 12 first hours of myocardial infarction
- **Contraindication**
 - *See under* Propranolol.
- **Precautions**
 - Breast-feeding: Appendix C
 - *See under* Propranolol.
 - Hepatic impairment: Appendix E
 - Pregnancy: Appendix B
- **Dose**

For prophylaxis of migraine

 - **ADULT:** *By mouth*, 100–200 mg daily in divided doses
- **Adverse effects**
 - *See under* Propranolol.

SECTION 8: Antineoplastic, immunosuppressive, and medicines used in palliative care

LML strengths and dosage forms are marked in colored text with an asterisk.

8.1 IMMUNOSUPPRESSIVE MEDICINES

Immunosuppressive drugs are used in organ transplant recipients to suppress rejection; they are also used as second-line drugs in chronic inflammatory conditions. Treatment should only be initiated by a specialist. Careful monitoring of blood counts is required in patients receiving immunosuppressive drugs and the dose should be adjusted to prevent bone marrow toxicity. Immunosuppressed patients are particularly prone to atypical infections.

Azathioprine is widely used in transplant recipients. It is useful when corticosteroid therapy alone has proven inadequate or for other conditions when a reduction in the dose of concurrently administered corticosteroids is required. It is metabolized to mercaptopurine and, as with mercaptopurine, doses need to be reduced when given with allopurinol. Toxic effects include myelosuppression and hepatic toxicity.

Ciclosporin is a potent immunosuppressant that is virtually free of myelotoxic effects, but is markedly nephrotoxic. It is particularly useful for the prevention of graft rejection and for the prophylaxis of graft-versus-host disease. The dose is adjusted according to plasma ciclosporin concentrations and renal function. Dose-related increases in serum creatinine and blood urea nitrogen (BUN) during the first few weeks may necessitate dose reduction.

Corticosteroids such as prednisolone have significant immunosuppressant activity and can also be used to prevent rejection of organ transplants.

- **Ciclosporin**

Ciclosporin is a complementary list immunosuppressive medicine.

- **Dosage form**

- *Capsules: 25 mg and 100 mg**
- Oral syrup: 100 mg/5 ml in 50 ml

- **Uses**

- Prevention of rejection in kidney, liver, heart, or bone marrow transplantation
- Graft-versus-host disease
- Nephrotic syndrome

- **Precautions**

- Monitor kidney function (dose-dependent increase in serum creatinine and urea during first few weeks post-transplant may necessitate dose reduction; exclude rejection in kidney transplant)
- Monitor liver function (adjust dosage according to bilirubin and liver enzymes): Appendix E
- Monitor blood pressure (discontinue if hypertension cannot be controlled by antihypertensive)
- Monitor serum potassium, particularly if marked renal impairment (risk of hyperkalemia)
- Monitor serum magnesium
- Hyperuricemia
- Measure blood lipids before and during treatment
- Avoid in porphyria
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

Additional precautions 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; not recommended for patients who also have uncontrolled infections or malignancy.

○ **Dose**

Note: Lower doses are required when ciclosporin is used with other immunosuppressants.

Organ transplantation, by mouth

- **ADULT** and **CHILD** over 3 months: 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 intravenous infusion over 2–6 hours

- **ADULT** and **CHILD:** One-third of the corresponding dose by mouth

Bone marrow transplantation, graft-versus-host disease, by mouth

- **ADULT** and **CHILD** over 3 months: 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 intravenous infusion over 2–6 hours

- **ADULT** and **CHILD** over 3 months: 3–5 mg/kg daily for 2 weeks, starting on the day before surgery, followed by maintenance by mouth

Nephrotic syndrome, by mouth

- **ADULT:** Initially 5 mg/kg daily in 2 divided doses

- **CHILD:** Initially 6 mg/kg daily in 2 divided doses
- Reduce dose in renal impairment; maximum 2.5 mg/kg daily
- After initial dose, slowly reduce 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).

Dilution and administration: According to manufacturer's directions

○ **Adverse effects**

- Dose-related and reversible increases in serum creatinine and urea unrelated to tissue rejection
- Burning sensation in hands and feet during initial therapy
- Electrolyte disturbances including hyperkalemia, and hypomagnesemia
- Hepatic dysfunction
- Hyperuricemia
- Hypercholesterolemia
- Hyperglycemia, hypertension (especially in heart transplant patients)
- Increased incidence of malignancies and lymphoproliferative disorders
- Increased susceptibility to infections due to immunosuppression
- Gastrointestinal disturbances
- Gingival hyperplasia
- Hirsutism
- Fatigue
- Allergic reactions
- Thrombocytopenia (sometimes with hemolytic uremic syndrome)
- Also mild anemia, tremors, convulsions, neuropathy
- Dysmenorrhea or amenorrhea, pancreatitis, myopathy, or muscle weakness
- Cramp
- Gout

- Edema
- Headache

8.2 CYTOTOXIC MEDICINE

The treatment of cancer with drugs, radiotherapy, and surgery is complex and should only be undertaken by an oncologist. For this reason, the following information is provided merely as a guide.

Chemotherapy may be curative or used to alleviate symptoms or to prolong life. Where the condition can no longer be managed with cytotoxic therapy, alternative palliative treatment (Section 8.4) should be considered.

For some tumors, single-drug chemotherapy may be adequate, but for most malignancies a combination of drugs provides the best response; specialist literature should be consulted. Cytotoxic drugs are often combined with other classes of drugs in the treatment of malignant conditions. Such drugs include hormone agonists and antagonists, corticosteroids, and immunostimulant drugs (Section 8.3). Combinations are, however, more toxic than single drugs.

As mentioned above, these are toxic drugs with should be used with great care and close monitoring. Treatment should be undertaken by specialists using approved regimens; specialist literature should be consulted for further information.

Precautions and contraindications

Treatment with cytotoxic drugs should be initiated only after baseline tests of liver and kidney function have been performed and baseline blood counts established. It may be necessary to modify or delay treatment in certain circumstances. The patient should also be monitored regularly during chemotherapy and cytotoxic drugs withheld if there is significant deterioration in bone marrow, liver, or kidney function.

Most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially in the first trimester. Contraceptive measures are required during therapy and possibly for a period after therapy has ended. Cytotoxic drugs are also contraindicated during breast-feeding. The risk of venous thromboembolism in cancer is increased by chemotherapy; prophylaxis against thromboembolism may be appropriate for patients receiving chemotherapy.

Cytotoxic drugs should be administered with care to avoid undue toxicity to the patient or exposure during handling by the health care provider.

Extravasation of intravenously administered cytotoxic drugs can result in severe pain and necrosis of the surrounding tissue. If extravasation occurs, aspiration of the drug should first be attempted, then the affected limb is elevated and warm compresses applied to speed and dilute the infusion or it is localized by applying cold compresses until the inflammation subsides; in severe cases, hydrocortisone cream may be applied topically to the site of inflammation.

Adverse effects

Cytotoxic drugs have considerable potential to damage normal tissue. Specific adverse effects apply, but a number are common to all cytotoxics, such as bone marrow and immunological suppression. Furthermore, the concomitant use of immunosuppressive drugs will enhance susceptibility to infections. Fever associated with neutropenia or immunosuppression requires immediate treatment with antibiotics.

Nausea and vomiting following administration of cytotoxic drugs and abdominal radiotherapy are often distressing and may compromise further treatment.

- **Fluorouracil**

Also known as 5-fluorouracil or 5FU. Fluorouracil is a complementary list cytotoxic medicine.

- **Dosage form**

- Injection: 50 mg/ml in 10 ml vial

- **Uses**

- Carcinomas of the colorectum, breast, stomach, pancreas, cervix, prostate, ovary, and endometrium
- Liver tumors
- Head and neck tumors
- Actinic keratosis

- **Contraindications**

- *See note above and consult specialist literature.*
- Pregnancy: Appendix B
- Breast-feeding: Appendix C

- **Precautions**

- *See note above and consult specialist literature.*
- Hepatic impairment: Appendix E
- ***Interactions:*** Appendix A

- **Dose**

- Consult specialist literature.

- **Adverse effects**

- Myelosuppression and palmar–plantar syndrome (erythema and painful desquamation of the hands and feet) mucositis and diarrhea
- Central neurotoxicity can also occur; for further information consult specialist literature.

- **Methotrexate**

Methotrexate is a complementary list cytotoxic medicine.

- **Dosage form**

- Tablet: 2.5 mg (as sodium salt)
- Injection: 50 mg (as sodium salt) in vial

- **Uses**

- Carcinoma of the breast, head and neck, and lung
- Trophoblastic tumors
- Acute lymphoblastic leukemia, meningeal leukemia
- Non-Hodgkin's lymphomas
- Advanced cases of mycosis fungoides
- Non-metastatic osteosarcoma
- Severe rheumatoid arthritis (Section 2.4)
- Crohn's disease

- **Contraindications**

- See Section 2.4.

- **Precaution**

- See Section 2.4.

- **Dose**

- Consult specialist literature.

- **Adverse effects**

- See Section 2.4.

8.3 HORMONES AND ANTIHORMONES

The corticosteroids prednisolone, dexamethasone, and hydrocortisone are synthetic hormones that may be given at pharmacological doses for certain malignancies, particularly hematological malignancies. Prednisolone is an important component of curative regimens for lymphomas and childhood leukemias, and for other cancers it has a palliative role.

- **Hydrocortisone**

Hydrocortisone is a complementary list medicine for the treatment of malignant neoplasms (Section 3.3).

- **Dosage form**

- Powder for injection: 100 mg (as sodium succinate) in vial and 25 mg/ml in 5 ml vial (as acetate) for preparing injectable solutions

- **Prednisolone**

Prednisolone is a representative corticosteroid. Various drugs can serve as alternatives. Prednisolone is a complementary list medicine for the treatment of malignant neoplasms.

- **Dosage form**

- Tablet: 5 mg

- **Uses**

- With antineoplastic drugs for acute lymphoblastic and chronic lymphocytic leukemias, Hodgkin's disease, and non-Hodgkin's lymphomas
 - Inflammatory and allergic reactions (Sections 3 and 18.1)
 - Inflammation of the eye (Section 21.2)

- **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 amebiasis, strongyloidiasis, or tuberculosis possibly reactivated
- Increased severity of viral infections, particularly chicken pox and measles (passive immunization with immunoglobulin required)
- Hypertension, recent myocardial infarction, congestive heart failure
- Elderly
- Children and adolescents (growth retardation, possibly reversible)
- Renal impairment: Appendix D
- Hepatic impairment: Appendix E
- Diabetes mellitus
- Osteoporosis
- Glaucoma, corneal perforation
- Severe psychosis, epilepsy
- Psoriasis
- Peptic ulcer
- Hypothyroidism
- History of steroid myopathy
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- ***Interactions:*** Appendix A.

○ **Dose**

Leukemias and lymphomas, by mouth

- **ADULT:** Initially up to 100 mg daily, then gradually reduced if possible to 20–40 mg daily
 - **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
- **Adverse effects**
- Gastrointestinal 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, sub-capsular cataracts, exacerbation of viral or fungal eye infections
 - Diabetes mellitus
 - Thromboembolism
 - Delayed tissue healing
 - Myopathy, muscle weakness of arms and legs
 - Depression, psychosis, epilepsy
 - Raised intracranial pressure
 - Hypersensitivity reactions

8.4 MEDICINES USED IN PALLIATIVE CARE

Palliative care includes both pain relief and the symptomatic relief of conditions including dyspnea, restlessness and confusion, anorexia, constipation, pruritus, nausea and vomiting, and insomnia.

Pain relief can be achieved with drugs and neurosurgical, psychological, and behavioral approaches adapted to individual patient needs. If carried out correctly, most patients with cancer pain can obtain effective relief. Pain is best treated with a combination of drug and non-drug measures. Some types of pain respond well to a combination of a non-opioid and an opioid analgesic.

Other types of pain are relieved by combining a corticosteroid and an opioid. Neuropathic pain often shows little response to non-opioids and opioids, but may be eased by tricyclic antidepressants and anticonvulsants. Cancer patients often have many fears and anxieties, and may become depressed. Very anxious or deeply depressed patients may need an appropriate psychotropic drug in addition to an analgesic. If this fact is not appreciated, the pain may remain intractable.

Medicines for neuropathic pain

Neuropathic pain often responds to a tricyclic antidepressant, such as amitriptyline, or to an anticonvulsant, such as carbamazepine or valproic acid; ketamine or lidocaine by intravenous infusion may be useful in some situations. Neuropathic pain may respond only partially to opioids, but they may be considered when other options fail. A corticosteroid may be required, particularly to relieve pain in patients with nerve compression.

SECTION 9: Anti-parkinsonism medicines

PARKINSONISM

The use of pharmacotherapy in Parkinsonism will depend upon the degree of incapacity of the patient and is generally not justified until symptoms compromise working ability and social relationships; levodopa is, however, used in the early stages in some patients. Close supervision is then needed to ensure that treatment regimens are tolerated and that appropriate changes are made to the regimen as the disease progresses.

The most effective form of therapy is a combination of levodopa and a peripheral dopa-decarboxylase inhibitor, such as carbidopa. The response to levodopa with carbidopa is a compromise between increased mobility and adverse effects. Dyskinesia may be dose-limiting and increasingly frequent with increased duration of treatment. Many factors, including tolerance and progression of the disease, may result in complications after 2–5 years of treatment. “End-of-dose” deterioration occurs when there is a reduced duration of benefit from a dose, resulting in disability and dystonias. The “on-off” phenomenon is characterized by large variations in motor performance, with normal function during the “on” period, and weakness and restricted mobility during the “off” period. Amelioration of these effects can sometimes be achieved by administering levodopa in a sustained-release preparation or in a greater number of fractionated doses throughout the day. Psychiatric symptoms including disruption of sleep, vivid dreams, and hallucinations are characteristic adverse effects that may occur at any time, especially in the elderly, and may require dose reduction or withdrawal of levodopa.

Treatment for idiopathic Parkinsonism is often initiated with a dopamine receptor-agonist such as bromocriptine. Supplementary use of amantadine, bromocriptine, or the monoamine-oxidase-B inhibitor selegiline can be of value either to enhance the effect of levodopa or to reduce end-of-dose fluctuations and on-off effects.

Anticholinergic (more correctly termed antimuscarinic) drugs such as biperiden are usually sufficient in drug-induced Parkinsonism.

Essential tremor and related disorders

Essential tremor. This can be treated with beta-blockers such as propranolol (120 mg daily), which may be of value if the tremor results in physical or social disability.

Dystonias. If no identifiable cause is found and the patient does not go into spontaneous remission, a trial of levodopa should be given to determine whether the patient has dopamine-responsive dystonia. If there is no response within 3 months, the drug should be withdrawn and small doses of an anticholinergic drug such as biperiden should be given. The dosage may be increased gradually and up to 16 mg daily may be tolerated. In patients who fail to respond to either levodopa or an anticholinergic, other drugs such as diazepam, baclofen, carbamazepine, or phenothiazines may be of value. Psychological treatments have also been used successfully in the management of dyskinesias.

Chorea. Choreiform movements can be induced by certain drugs, including levodopa, phenytoin, and antipsychotic drugs. Huntington's disease is the most common of the hereditary choreas. Drug treatment is symptomatic and does not alter the progression of the disease. The aim of therapy is to reduce dopaminergic transmission, which results from excessive or enhanced cholinergic activity. Antipsychotic drugs antagonize dopamine and usually lessen the chorea temporarily.

Tics. Tics that resemble choreiform movements are commonly associated with anxiety. However, in the more complex multiple tic disorder Tourette's syndrome, treatment with antipsychotic drugs may be required.

Tardive dyskinesia. This is associated with chronic administration of antipsychotic drugs. It is characterized by involuntary, repetitive, choreiform movement of the cheek, mouth, and fingers. The first step of treatment should always be discontinuation of the antipsychotic drug or dosage reduction if the underlying psychotic disorder permits.

LML strengths and dosage forms are marked in *italic* with an asterisk.

- **Biperiden**

Biperiden is a representative anticholinergic and various drugs can serve as alternativea.

- **Dosage form**

- Injection: 5 mg (lactate) in 1 ml ampoule
- Tablet: 2 mg (hydrochloride)

- **Uses**

- Drug-induced extrapyramidal symptoms (but not tardive dyskinesia) and adjunctive treatment of Parkinsonism

- **Contraindications**

- Angle-closure glaucoma
- Untreated urinary retention
- Prostatic hypertrophy
- Myasthenia gravis
- Gastrointestinal obstruction

- **Precautions**

- Elderly
- Cardiovascular disease
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Avoid abrupt withdrawal
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- ***Interactions:*** Appendix A

- **Skilled tasks:** May impair ability to perform skilled tasks (for example, operating machinery or driving)

- **Dose**

Drug-induced extrapyramidal symptoms, Parkinsonism, by mouth

- **ADULT:** Initially 1 mg twice daily, increased gradually to 2 mg 3 times daily; usual maintenance dose, 3–12 mg daily in divided doses

Drug-induced extrapyramidal symptoms, Parkinsonism, by intramuscular injection or slow intravenous injection

- **ADULT:** 2.5–5 mg repeated as necessary; maximum 20 mg in 24 hours

- **Adverse effects**

- Drowsiness, dry mouth, constipation, blurred vision
- Hesitancy of micturition, dizziness, tachycardia, arrhythmias
- Confusion, excitement, agitation, hallucinations, and psychiatric disturbances with high dosage, especially in the elderly and other susceptible patients (may require withdrawal of treatment)
- Impaired memory

- **Bromocriptine**

- **Dosage form**

- Tablet 2.5 mg

- **Uses**

- Parkinson's disease
- Prevention or suppression of lactation
- Hypogonadism, galactorrhea, infertility
- Acromegaly, prolactinoma

- **Contraindications**

- Bromocriptine should not be used in patients with hypersensitivity to ergot alkaloids or those with cardiac valvulopathy (exclude before treatment).
- Also hypertension in postpartum women or in puerperium
- ***Postpartum or puerperium:*** Should not be used postpartum or in puerperium in women with high blood pressure, coronary artery disease, or symptoms (or history) of serious mental disorder; monitor blood pressure carefully (especially during first few days) in postpartum women; very rarely hypertension, myocardial infarction, seizures or stroke (both sometimes preceded by severe headache or visual disturbances) occurs, and mental disorders have been reported in postpartum women given bromocriptine for lactation suppression—use caution with antihypertensive therapy and avoid other ergot alkaloids; discontinue immediately if hypertension, unremitting headache, or signs of CNS toxicity develops.

- **Precautions**

- Monitor for pituitary enlargement, particularly during pregnancy.
- Monitor visual field to detect secondary field loss in macroprolactinoma.
- Contraceptive advice if appropriate (oral contraceptives may increase prolactin concentration)
- Renal impairment: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- ***Interactions:*** Appendix A

- **Dose**

Parkinson's disease

- First week: 1–1.25 mg at night
- Second week: 2–2.5 mg at night

- Third week: 2.5 mg twice daily
- Fourth week: 2.5 mg, 3 times daily, then increasing by 2.5 mg every 3–14 days according to response to a usual range of 10–30 mg daily

Patient advice: Take with food.

Prevention or suppression of lactation

- Prevention: Initially, 2.5 mg on day 1, then 2.5 mg twice daily for 14 days
- Suppression: Daily for 2–3 days, then 2.5 mg twice daily for 14 days

Hypogonadism, galactorrhea, infertility

- Initially 1–1.25 mg at bedtime, increased gradually
- Usual dose: 7.5 mg daily in divided doses, increased if necessary to maximum 30 mg daily, usual dose in infertility without hyperprolactinemia, 2.5 mg twice daily

Acromegaly

- Initially 1–1.25 mg at bedtime, increased gradually to 5 mg every 6 hours

Prolactinoma

- Initially 1–1.25 mg at bedtime, increased gradually to 5 mg every 6 hours (occasional patients may require up to 30 mg daily)

- **CHILD** under 15 years: Not recommended

○ **Adverse effects**

- Nausea, constipation, and headache are common side effects of bromocriptine.
- Paraesthesia has been reported rarely.
- Other reported side effects include hypotension (hypotensive reactions can be disturbing in some patients during the first few days of treatment with

bromocriptine—monitor blood pressure for a few days after starting treatment and follow dosage increases; particular care should be exercised when driving or operating machinery), dyskinesia, pathological gambling, increased libido, hypersexuality, leg cramps, allergic skin reactions, alopecia, and peripheral edema.

- Bromocriptine has been associated with pleuritis, pleural effusion, cardiac valvulopathy, pericardial effusion, constrictive pericarditis, and retroperitoneal, pleural and pulmonary fibrosis.
- Also nasal congestion
- Less commonly vomiting, postural hypotension, fatigue, dizziness, dry mouth
- Also, particularly with high doses: confusion, psychomotor excitation, hallucinations
- Rarely diarrhea, gastrointestinal bleeding, gastric ulcer, abdominal pain, tachycardia, bradycardia, arrhythmia, insomnia, psychosis, visual disturbances, tinnitus
- Very rarely vasospasm of fingers and toes, particularly in patients with Raynaud's syndrome, and effects like neuroleptic malignant syndrome on withdrawal
- Urinary incontinence, leukopenia, thrombocytopenia, hyponatremia, reversible hearing loss

- **Levodopa + carbidopa**

Carbidopa is a representative peripheral dopa-decarboxylase inhibitor. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 100 mg + 10 mg; 250 mg + 25 mg; and 250 mg + 50 mg

- **Uses**

- All forms of Parkinsonism other than drug-induced

- **Contraindications**

- Concurrent use of monoamine oxidase inhibitors
- Angle-closure glaucoma
- Confirmed or suspected malignant melanoma

- **Precautions**

- Pulmonary disease, peptic ulceration, cardiovascular disease (including previous myocardial infarction)
- Diabetes mellitus, osteomalacia, open-angle glaucoma, history of melanoma (risk of activation), psychiatric illness (avoid if severe)
- Close monitoring of hepatic, hematological, psychiatric, cardiovascular, and renal function required in long-term therapy
- Elderly
- Avoid rapid dose increases
- Warn patients to resume normal activities gradually
- Avoid abrupt withdrawal
- Pregnancy (toxicity in animals): Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Dose**

Parkinsonism, by mouth

- **ADULT:** Expressed in terms of levodopa, initially 100 mg (with carbidopa 10 mg) twice daily, increased by 100 mg (with carbidopa 10 mg) every few days as necessary, to a maximum of levodopa 1.5 g

Administration: Optimum daily dose must be determined for each patient by careful monitoring and be taken after meals.

Note: Carbidopa, 70–100 mg daily, is necessary for full inhibition of peripheral dopa-decarboxylase.

- **Adverse effects**

- Nausea, anorexia, and vomiting, particularly at the start of treatment
- Postural hypotension at the start of treatment, particularly in the elderly and those receiving antihypertensives
- Excessive drowsiness and sudden onset of sleep (warn patient of these effects)
- Confusion, vivid dreams, dizziness, tachycardia, arrhythmias
- Reddish discoloration of body fluids
- Insomnia, headache, flushing, gastrointestinal bleeding, peripheral neuropathy
- Taste disturbances, pruritus, rash, liver enzyme changes
- Psychiatric symptoms including psychosis, depression, and hallucinations
- Delusions and neurological disturbances including dyskinesias (may be dose-limiting)
- Painful dystonic spasms (end-of-dose effects) and (on-off effects) after prolonged treatment (*see note above*)
- Neuroleptic malignant syndrome (on sudden withdrawal)
- Rarely hypersensitivity

- **Trihexyphenidyl**

- **Dosage form**

- Tablet: 2 mg (as hydrochloride)

- **Uses**

- Parkinsonism
- Drug-induced extrapyramidal symptoms (but not tardive dyskinesia)

- **Contraindication**

- Antimuscarinics should be avoided in gastrointestinal obstruction and myasthenia gravis.

○ **Precautions**

- Antimuscarinics should be used with caution in cardiovascular disease, hypertension, psychotic disorders, prostatic hypertrophy, pyrexia, in those susceptible to angle-closure glaucoma, and in the elderly.
- Antimuscarinics should not be withdrawn abruptly in patients receiving long-term treatment.
- Antimuscarinics are liable to abuse.
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix B
- Breast-feeding: Appendix C.
- **Interactions:** Appendix A
- **Skilled tasks:** May affect performance of skilled tasks (for example, driving)

○ **Dose**

- 1 mg daily, increased gradually; usual maintenance dose 5–15 mg daily in 3–4 divided doses (max. 20 mg daily), maintenance dose is 5–15 mg per day in 3–4 divided doses
- **ELDERLY:** Preferably lower end of range

Dystonia, by mouth

- **CHILD** 1 month–18 years: 1–2 mg daily in 1–2 divided doses

○ **Adverse effects**

- Constipation, dry mouth, nausea, vomiting, tachycardia, dizziness, confusion, euphoria, hallucinations, impaired memory, anxiety, restlessness, urinary retention, blurred vision, and rash.
- Angle-closure glaucoma may occur very rarely.

SECTION 10: Medicines affecting the blood

LML strengths and dosage forms are marked in *italic* with an asterisk.

10.1 ANTI-ANEMIA MEDICINES

Iron-deficiency anemia

Anemia occurs when the blood hemoglobin concentration falls below the normal range for the age and sex of the individual. It has many different etiologies and therefore it is essential that a correct diagnosis is made before initiating therapy. Any serious underlying cause of iron-deficiency anemia, including gastric erosion and gastrointestinal cancer, should be excluded before giving iron replacement.

Prophylaxis with iron salts is justifiable in individuals who have additional risk factors for iron deficiency (for example, dietary deficiency). Prophylaxis may also be appropriate in malabsorption, menorrhagia, after subtotal or total gastrectomy, and in hemodialysis patients.

Supplementation with iron and folic acid is recommended by WHO for all pregnant women; in addition, where prevalence of anemia is above 40%, it is recommended that women of childbearing age and breast-feeding women should be given 3 months of iron and folic acid supplementation.

Low-birth-weight infants, including preterm neonates, should receive iron supplementation between the ages of 2 and 23 months. Iron supplementation should also be given to all children aged 6–23 months if their diet does not include foods fortified with iron or if prevalence of anemia is above 40%. Children aged 24 months and above should receive a 3-month course of iron supplementation (with folic acid if above 5 years) if the local prevalence of anemia is above 40%.

Iron should be given orally wherever possible. **Ferrous salts** are preferred as non-ferric salts are much less well absorbed. Preparations containing ferrous salts differ only marginally in efficiency of absorption and thus the choice of preparation is usually decided by the incidence of adverse effects and cost. The oral dose of elemental iron for treatment of iron-deficiency anemia in adults should be in the range of 100–200 mg daily, taken with meals.

The approximate elemental iron content of various ferrous salts is:

- Ferrous fumarate 210 mg (68 mg iron)
- Ferrous gluconate 300 mg (35 mg iron)
- Ferrous succinate 100 mg (35 mg iron)
- Ferrous sulfate 300 mg (60 mg iron)
- Dried ferrous sulfate 200 mg (65 mg iron)

The hemoglobin concentration should rise by about 100–200 mg/100 ml per day or by 2 g/100 ml over 3–4 weeks. After the hemoglobin has risen to normal, treatment should be continued for a further 3 months to replenish the body's iron stores.

Iron intake in the evening has been reported to improve its absorption. Iron intake with meals may reduce bioavailability but may improve tolerability and adherence.

If adverse effects occur, either the dosage can be reduced or an alternative ferrous salt used, but an improvement in tolerance may be due to lower intake of elemental iron. Gastrointestinal irritation may occur with iron salts. Nausea and epigastric pain are dose-related. Iron preparations taken orally may be constipating, particularly in the elderly, occasionally leading to fecal impaction. Oral iron may exacerbate diarrhea in patients with inflammatory bowel disease, but care is also needed in patients with intestinal strictures and diverticular disease. Iron as iron dextran (a complex of ferric hydroxide with dextrans) or iron sucrose (a complex of ferric hydroxide with sucrose) may be given parenterally if the patient cannot tolerate oral iron, or does not take it reliably or if there is continuing severe blood loss or malabsorption. Many patients with chronic renal failure

who are receiving hemodialysis (and some on peritoneal dialysis) require intravenous iron on a regular basis. However, parenteral iron may cause more harm than benefit. With the exception of patients on hemodialysis the hemoglobin response is not significantly faster with the parenteral route than the oral route.

Megaloblastic anemias

Megaloblastic anemias result from a lack of either vitamin B12 (hydroxocobalamin) or folate or both. The clinical features of folate-deficient megaloblastic anemia are similar to those of vitamin B12 deficiency except that the accompanying severe neuropathy does not occur; it is essential to establish the underlying cause in every case.

Hydroxocobalamin is used to treat vitamin B12 deficiency whether due to dietary deficiency or malabsorption (including pernicious anemia). Pernicious anemia is due to a lack of intrinsic factor, which is essential for vitamin B12 absorption.

Folate deficiency due to poor nutrition, pregnancy, use of anti-epileptics, or malabsorption is treated with **folic acid**. Folic acid should not, however, be administered without vitamin B12 in undiagnosed megaloblastic anemia because of the risk of precipitating neurological changes due to the underlying vitamin B12 deficiency.

Preparations containing **a ferrous salt** and **folic acid** are used for the prevention of megaloblastic anemia in pregnancy. The low doses of folic acid in these preparations are inadequate for the treatment of megaloblastic anemias.

Prevention of neural tube defects

An adequate intake of **folic acid** before conception and during early pregnancy reduces the risk of neural tube defects in babies. Therefore, women planning a pregnancy should receive sufficient folic acid before conception and in the first 12 weeks of pregnancy; folic acid may be given as a food or as a medicinal supplement in a dose of 400–500 micrograms daily. A woman who has not received supplementary folic acid and suspects that she might be pregnant should start taking folic acid at once and continue until week

12 of pregnancy. Women at increased risk of giving birth to a baby with neural tube defects (for example, history of neural tube defect in a previous child) should receive a higher dose of folic acid, approximately 5 mg daily, starting before conception and continuing for 12 weeks after conception. Women taking anti-epileptic medication should be counseled by their doctor before starting folic acid.

- **Ferrous salts**

- **Dosage form**

- Tablets: 50 mg and 60 mg (ferrous sulfate)
 - Oral liquid: 125 mg/5 ml, in 120 ml (ferrous sulfate)
 - *Oral drops: 25 mg/ml (ferrous sulfate)**
 - *Tablets 160 mg and 250 mg (ferrous gluconate)**

- **Uses**

- Iron-deficiency anemia

- **Contraindications**

- Hemosiderosis, hemochromatosis
 - Any form of anemia not caused by iron deficiency
 - Patients receiving repeated blood transfusions
 - Parenteral iron therapy

- **Precautions**

- Should not be administered longer than 6 months
 - Pregnancy
 - Peptic ulcer, regional enteritis, ulcerative colitis, intestinal strictures, diverticula
 - ***Interactions:*** Appendix A

- **Dose**

Iron-deficiency anemia, by mouth

- **ADULT:** Elemental iron, 100–200 mg daily in divided doses

Prevention of iron-deficiency anemia (in those at particular risk), by mouth

- **ADULT** (woman): Elemental iron 60 mg daily
- **CHILD** under 5 years: Elemental iron, 2 mg/kg daily (max. 30 mg)
- **CHILD** over 5 years: Elemental iron, 30 mg daily
- In women and children over 5 years, folic acid may also be given.

Patient advice: Although iron preparations are best absorbed on an empty stomach, they may be taken after food to reduce gastrointestinal adverse effects; they may discolor 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).

- **Adverse effects**

- Constipation, diarrhea, dark stools, nausea, epigastric pain, gastrointestinal irritation
- Long-term or excessive administration may cause hemosiderosis

- **Ferrous sulfate + folic acid**

- **Dosage form**

- Tablets: 60 mg + 0.4 mg, 100 mg + 0.35 mg, 150 mg + 0.5 mg, and 200 mg + 0.25 mg

- **Uses**

- Prevention of iron and folic acid deficiencies in pregnancy

Note: Low doses of folic acid in the combination preparations above are inadequate for treatment of megaloblastic anemia.

- **Precautions**

- Overdosage: *See* Section 4.2
- **Interactions:** Appendix A

- **Dose**

Severe anemia, by mouth

- **ADULT:** Elemental iron, 120 mg + folic acid 400 micrograms daily for 3 months
- **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

Prevention of iron and folate deficiencies in pregnancy, by mouth

- **ADULT:** Elemental iron, 100 mg + folic acid, 350–400 micrograms daily throughout pregnancy

- **Adverse effects**

- *See* Ferrous salts.

- **Folic acid**

- **Dosage form**

- Tablets: 1 mg and 5 mg

- **Uses**

- Treatment of folate-deficiency megaloblastic anemia
- Prevention of neural tube defects in pregnancy

- **Contraindications**

- Should never be given without vitamin B12 in undiagnosed megaloblastic anemia or other vitamin B12 deficiency states because of the risk of precipitating sub-acute combined degeneration of the spinal cord
- Folate-dependent malignant disease

- **Precautions**

- Women receiving anti-epileptic therapy (need counseling before starting folic acid, *see also* note above)
- **Interactions:** Appendix A

- **Dose**

Treatment of folate-deficiency, megaloblastic anemia, by mouth

- **ADULT:** 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, by mouth

- **ADULT:** 400–500 micrograms daily before conception and during the first 12 weeks of pregnancy

Prevention of recurrence of neural tube defects, by mouth

- **ADULT:** 5 mg daily (reduced to 4 mg daily, if suitable preparation available) from at least 4 weeks before conception until 12th week of pregnancy

- **Hydroxocobalamin**

- **Dosage form**

- Injection: 0.5 mg/ml and 1 mg/ml in 1 ml ampoule

- **Uses**

- Megaloblastic anemias due to vitamin B12 deficiency

- **Precautions**

- Except in emergencies, should not be given before diagnosis confirmed
- Monitor serum potassium levels (arrhythmias secondary to hypokalemia in early therapy).

- **Dose**

Megaloblastic anemia without neurological involvement, by intramuscular injection

- **ADULT** and **CHILD**: Initially 1 mg 3 times a week for 2 weeks, then 1 mg every 3 months

Megaloblastic anaemia with neurological involvement, by intramuscular injection

- **ADULT** and **CHILD**: Initially 1 mg on alternate days until no further improvement occurs, then 1 mg every 2 months

Prophylaxis of macrocytic anemias, by intramuscular injection

- **ADULT** and **CHILD**: 1 mg every 2–3 months

Tobacco amblyopia and Leber optic atrophy, by intramuscular injection

- **ADULT** and **CHILD**: 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months

- **Adverse effects**

- Nausea, headache, dizziness
- Fever, hypersensitivity reactions including rash and pruritus
- Pain at injection site
- Hypokalemia during initial treatment

- **Iron dextran**

- **Dosage form**

- Injection: 50 mg/ml (a complex of ferric hydroxide with dextran containing 5% of iron) in 2 ml ampoule

- **Uses**

- Iron-deficiency anemia

- **Precautions**

- Oral iron not to be given until 5 days after last injection
 - **Anaphylaxis:** Anaphylactic reactions can occur with parenteral iron and a test dose is recommended before *each* dose; the patient should be carefully observed for 60 minutes after the first test dose and for 15 minutes after subsequent test doses (subsequent test doses not necessary for intramuscular administration). Facilities for cardiopulmonary resuscitation must be available; risk of allergic reactions increased in immune or inflammatory conditions.

- **Contraindications**

- History of allergic disorders including asthma, and eczema
 - Active rheumatoid
 - Arthritis
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Pregnancy: Appendix B

- **Dose**

- By slow intravenous injection or by intravenous infusion*

- **ADULT** over 18 years: Calculated according to body weight and iron deficit, consult product literature
 - **CHILD** under 14 years: Not recommended

- **Adverse effects**

- Less commonly nausea, vomiting, constipation, abdominal pain, dyspnea, dysphonia, flushing, numbness, fever, cramps, blurred vision, pruritus, rash, hypersensitivity reactions (including anaphylaxis), injection-site reactions
- Rarely diarrhea, angioedema, tachycardia, arrhythmias, hypotension, chest pain, malaise, seizures, tremor, dizziness, restlessness, loss of consciousness, altered mental status, myalgia, arthralgia, sweating
- Very rarely hypertension, fetal bradycardia, palpitation, headache, paresthesia, hemolysis, transient deafness

10.2 MEDICINES AFFECTING COAGULATION

Anticoagulants are used to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells. They are therefore used widely in the prevention and treatment of deep-vein thrombosis in the legs, prophylaxis of embolization in rheumatic heart disease, and atrial fibrillation and to prevent thrombi forming on prosthetic heart valves.

Heparin sodium is a parenteral anticoagulant that initiates anticoagulation rapidly but has a short duration of action. The low-molecular-weight heparins have a longer duration of action. For patients at high risk of bleeding, heparin sodium is more suitable than the low-molecular-weight heparins because its effect can be terminated rapidly by stopping the infusion.

For the treatment of deep venous thrombosis and pulmonary embolism heparin sodium is given as an intravenous loading dose, followed by continuous intravenous infusion (using an infusion pump) or by intermittent subcutaneous injection. An oral anticoagulant is started at the same time as the heparin. The heparin needs to be continued for at least 5 days, until the oral anticoagulant has taken effect and the prothrombin time (usually

reported as the international normalized ratio, or INR) has been in the therapeutic range for 2 consecutive days. Laboratory monitoring is essential on a daily basis. Heparin sodium is also used in regimens for the management of myocardial infarction, the management of unstable angina, acute peripheral arterial occlusion, and in dialysis.

In patients undergoing general surgery, low-dose heparin by subcutaneous injection is used to prevent postoperative deep-vein thrombosis and pulmonary embolism in high-risk patients (those with obesity, malignant disease, history of deep-vein thrombosis or pulmonary embolism, patients over 40 years, those with an established thrombophilic disorder or those undergoing major or complicated surgery). It is also of value in high-risk medical patients—for example, those who are obese, have heart failure, or are confined to bed.

If hemorrhage occurs, it is usually sufficient to withdraw heparin, but if rapid reversal of the effects of heparin is required, **protamine sulfate** is a specific antidote. When oral anticoagulants are given, it takes at least 48–72 hours for the anticoagulant effect to develop fully; if an immediate effect is needed, heparin must be given concomitantly.

Warfarin is indicated in deep-vein thrombosis, pulmonary embolism, for patients with atrial fibrillation who are at risk of embolization, and for those with mechanical prosthetic heart valves (to prevent emboli from developing on the valves); oral anticoagulants should not be used as first-line therapy in cerebral thrombosis or peripheral arterial occlusion. The main adverse effect of oral anticoagulants is hemorrhage. Prothrombin time should be checked on a daily basis initially, and then at longer intervals depending on response. If severe hemorrhage occurs, stop warfarin and give **phytomenadione** (vitamin K) by slow intravenous injection.

Anticoagulants in pregnancy

Oral anticoagulants are teratogenic and should not be given in the first trimester of pregnancy. Women at risk of pregnancy should be warned of this danger since stopping warfarin before the sixth week of gestation may largely avoid the risk of fetal abnormality. Oral anticoagulants cross the placenta, giving rise to the risk of placental or

fetal hemorrhage, especially during the last few weeks of pregnancy and at delivery. Therefore, if at all possible, oral anticoagulants should be avoided in pregnancy, especially in the first and third trimester. Difficult decisions may have to be made, particularly in women with prosthetic heart valves or with a history of recurrent venous thrombosis or pulmonary embolism.

Hemophilia

Desmopressin by injection may aid hemostasis and be useful in mild forms of hemophilia. For minor procedures, including dental surgery, it may circumvent the need for factor VIII. For the use of factor VIII and factor IX in hemophilia, *see* Section 11.2.

- **Enoxaparin sodium**

- **Dosage form**

- Injection solution: 100 mg/ml in 1 ml ampoule

- **Uses**

- Prophylaxis of deep-vein thrombosis
- Treatment of deep-vein thrombosis or pulmonary embolism
- Treatment of acute ST-segment elevation myocardial infarction

- **Contraindication**

- *See under* Heparin.

- **Precautions**

- *See under* Heparin and notes above.
- Low body weight (increased risk of bleeding)
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix B
- Breast-feeding: Appendix C

- **Interactions:** Appendix A

- **Dose**

Dose prophylaxis of deep-vein thrombosis especially in surgical patients, by subcutaneous injection, moderate risk

- **ADULT:** 20 mg (2,000 units) approximately 2 hours before surgery, then 20 mg (2,000 units) every 24 hours; high risk (e.g., orthopedic surgery), 40 mg (4,000 units) 12 hours before surgery, then 40 mg (4,000 units) every 24 hours

Prophylaxis of deep-vein thrombosis in medical patients, by subcutaneous injection

- **ADULT:** 40 mg (4,000 units) every 24 hours

Treatment of deep-vein thrombosis or pulmonary embolism, by subcutaneous injection

- **ADULT:** 1.5 mg/kg (150 units/kg) every 24 hours until adequate oral anticoagulation established

Treatment of acute ST-segment elevation myocardial infarction

- **ADULT** under 75 years: *By intravenous injection*, 30 mg (3,000 units) followed by *subcutaneous injection*, 1 mg/kg (100 units/kg), then by *subcutaneous injection*, 1 mg/kg every 12 hours for up to 8 days (max. 100 mg [10,000 units] for first two subcutaneous doses only)
- **ELDERLY** over 75 years: *By subcutaneous injection only*, 750 micrograms/kg (75 units/kg) every 12 hours (maximum 75 mg [7,500 units] for first 2 doses only)
- Patients undergoing percutaneous coronary intervention, additional dose, *by intravenous injection*, 300 micrograms/kg (30 units/kg) at time of procedure if last subcutaneous dose given more than 8 hours previously

Note: When administered in conjunction with a thrombolytic, enoxaparin should be given between 15 minutes before and 30 minutes after the start of thrombolytic therapy.

Unstable angina and non-ST-segment-elevation myocardial infarction, by subcutaneous injection

- **ADULT:** 1 mg/kg (100 units/kg) every 12 hours usually for 2–8 days (min. 2 days)

Prevention of clotting in extracorporeal circuits

- Consult product literature.

Treatment of venous thromboembolism in pregnancy (unlicensed indication), by subcutaneous injection

- Early pregnancy body weight under 50 kg: 40 mg (4,000 units) twice daily; body weight 50–70 kg, 60 mg (6,000 units) twice daily; body weight 70–90 kg, 80 mg (8,000 units) twice daily; body weight over 90 kg, 100 mg (10,000 units) twice daily

- **Adverse effects**

- See under Heparin.

- **Heparin sodium**

- **Dosage form**

- Injection solution 1,000 IU/ml and 2,500 IU/ml in 5 ml ampoules and 5,000 IU/ml in 1 ml ampoules

- **Uses**

- Treatment and prophylaxis of deep-vein thrombosis and pulmonary embolism

- Unstable angina (Section 12.1)
- Ischemic stroke (Section 12.5)
- **Contraindications**
 - Hypersensitivity to heparin
 - Hemophilia and other hemorrhagic disorders, thrombocytopenia, peptic ulcer, recent cerebral hemorrhage, 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: Appendix E
 - Renal failure: Appendix D
 - Elderly
 - Hypersensitivity to low-molecular-weight heparins
 - Spinal or epidural anesthesia (risk of spinal hematoma)
 - Pregnancy: Appendix B
 - Diabetes mellitus, acidosis, concomitant potassium-sparing drugs (increased risk of hyperkalemia)
 - **Interactions:** Appendix A
- **Dose**

Treatment of deep-vein thrombosis and pulmonary embolism and unstable angina, by intravenous injection

- **ADULT:** Loading dose of 5,000 IU (10,000 IU in severe pulmonary embolism) followed by *continuous intravenous infusion* of 15–25 IU/kg/hour or by *subcutaneous injection* of 15,000 IU every 12 hours; laboratory monitoring is essential, preferably on a daily basis and dose adjusted accordingly.

- **SMALL ADULT and CHILD:** *By intravenous injection*, lower loading dose, then *by continuous intravenous infusion*, 15–25 IU/kg/hour or *by subcutaneous injection*, 250 IU/kg every 12 hours

Prophylaxis in general surgery, by subcutaneous injection

- **ADULT:** 5,000 IU 2 hours before surgery, then every 8–12 hours for 7 days or until patient is ambulant (monitoring not needed)
- **PREGNANT WOMAN:** 5,000–10,000 IU every 12 hours

Note: Not intended to cover prosthetic heart valve management in pregnancy, which requires specialist management

- **Adverse effects**

- Immune-mediated thrombocytopenia usually develops 6–10 days after commencement of therapy (requires immediate withdrawal of heparin)
- Hemorrhage, skin necrosis, hypersensitivity reactions including urticaria, angioedema, and anaphylaxis
- Osteoporosis after prolonged use and rarely alopecia

- **Phytomenadione / vitamin K**

- **Dosage form**

- Injection: 10 mg/ml in 1 ml ampoule
- Tablet: 10 mg

- **Uses**

- Antagonist to warfarin
- Treatment and prophylaxis against hemorrhagic disease of the newborn

- **Precautions**

- Elderly (reduce dose)
- Hepatic impairment: Appendix E

- Not an antidote to heparin
- Pregnancy: Appendix B
- **Interactions:** Appendix A

○ **Dose**

Warfarin-induced hypoprothrombinemia; no bleeding or minor bleeding, by slow intravenous injection

- **ADULT:** 500 micrograms or by mouth, up to 5 mg

Moderate hemorrhage, by mouth or by intramuscular injection

- **ADULT:** 10–20 mg

Severe hemorrhage, by slow intravenous injection

- **ADULT:** 5–10 mg

Treatment of hemorrhagic disease of the newborn, by intravenous or intramuscular injection

- **NEONATE:** 1 mg, with further doses if necessary at 8-hour intervals

Prophylaxis of hemorrhagic disease of the newborn, by intramuscular injection

- **NEONATE:** 0.5–1 mg as single dose or *by mouth*, 2 mg, followed by a second dose after 4–7 days and for breast-fed babies a third dose after 1 month

○ **Adverse effects**

- Hypersensitivity reactions including flushing, dyspnea, bronchospasm, dizziness, hypotension, and respiratory or circulatory collapse (which may be due to the polyethoxylated castor oil surfactant used in some injection formulations rather than due to phytomenadione)

SECTION 11: Blood products and plasma substitutes

Fluid requirements including that for blood must be assessed before, during, and after major surgery. Replacement fluids should correspond as nearly as possible in volume and composition to those lost. Blood transfusion is essential to restore oxygen-carrying capacity when more than 15% of the circulating blood volume is lost, but should be avoided whenever screening for human immunodeficiency viruses and hepatitis B virus is impracticable.

Isotonic sodium chloride solution may be used for short-term volume replacement. Plasma expanders such as dextran 70 or polygeline may be useful. Provided renal function is maintained, fluid is most simply replaced by intravenous administration of sodium chloride solution (sodium chloride, 9 mg/ml or 0.9%) or the more physiologically appropriate compound solution of sodium lactate.

In medical emergencies, there is usually an existing fluid deficit that must be assessed and corrected before surgery. Isotonic glucose/sodium chloride mixtures (most commonly, a mixture of glucose, 4% and sodium chloride, 0.18%) are preferred in children but injudicious use of such fluids may cause dilutional hyponatremia, especially following illness or injury, which increase the secretion of antidiuretic hormones.

When fluids are administered intravenously for more than 24 hours, potassium chloride (Section 26.2) is required to prevent potassium depletion. In order to avoid serious arrhythmias, especially in patients with impaired renal function, the required dose of potassium should be determined, whenever possible, by monitoring plasma concentrations of potassium. *See also* Section 26.

11.1 PLASMA SUBSTITUTES

Dextran 70 and polygeline are macromolecular substances that are metabolized slowly; they may be used to expand and maintain blood volume in shock arising from conditions such as burns or septicemia. They are rarely needed when shock is due to sodium and

water depletion, as, in these circumstances the shock responds to water and electrolyte repletion. Plasma substitutes should not be used to maintain plasma volume in conditions such as burns or peritonitis, where there is loss of plasma protein, water, and electrolytes over periods of several days. In these situations, plasma or plasma protein fractions containing large amounts of albumin should be given.

Plasma substitutes may be used as an immediate short-term measure to treat massive hemorrhage until blood is available, but large volumes of some plasma substitutes can increase the risk of bleeding by depleting coagulation factors. Dextran may interfere with blood group cross-matching or biochemical measurements, and therefore these should be carried out before the infusion is started. Plasma substitutes are often used in very ill patients whose condition is unstable. Close monitoring is required, and fluid and electrolyte therapy should be adjusted according to the patient's condition at all times.

- **Dextran 70**

Dextran is a representative plasma substitute. Various preparations can serve as alternatives (polygeline, 3.5% solution for injection is considered equivalent).

- **Dosage form**

- Injectable solution: 6%

- **Uses**

- Short-term blood volume expansion

- **Contraindications**

- Severe congestive heart failure
- Renal failure
- Bleeding disorders such as thrombocytopenia and hypofibrinogenemia

- **Precautions**

- Cardiac disease

- Liver disease: Appendix E
- Renal impairment: Appendix D
- Monitor urine output
- Avoid hematocrit falling below 25–30%
- Where possible, monitor central venous pressure
- Can interfere with blood group cross-matching and biochemical tests (take samples before start of infusion)
- Monitor for hypersensitivity reactions
- Pregnancy: Appendix B

○ **Dose**

Short-term blood volume expansion, by rapid intravenous infusion

- **ADULT:** 500–1,000 ml initially, followed by a further 500 ml if necessary (total dosage should not exceed 20 ml/kg during the initial 24 hours); if required, 10 ml/kg daily may be given for a further 2 days (treatment should not continue for longer than 3 days)
- **CHILD:** Total dosage should not exceed 20 ml/kg

○ **Adverse effects**

- Hypersensitivity reactions including fever, nasal congestion, joint pains, urticaria, hypotension, bronchospasm, and rarely, severe anaphylactoid reactions
- Transient increase in bleeding time

11.2 PLASMA FRACTIONS FOR SPECIFIC USE

Blood coagulation factors

Factor VIII is essential for blood clotting and the maintenance of effective hemostasis; von Willebrand factor is a mediator in platelet aggregation and also acts as a carrier for factor VIII. Blood coagulation factors VII, IX, and X are essential for the conversion of factor II (prothrombin) to thrombin. Deficiency in any of these factors results in hemophilia.

Bleeding episodes in hemophilia require prompt treatment with replacement therapy.

Factor VIII, used for the treatment of hemophilia A, is a sterile freeze-dried powder containing the blood coagulation factor VIII fraction prepared from pooled human venous plasma. Standard factor VIII preparations also contain von Willebrand factor and may be used to treat von Willebrand disease. Highly purified preparations, including recombinant factor VIII, are available; they are indicated for the treatment of hemophilia A but do not contain sufficient von Willebrand factor for use in the management of von Willebrand disease.

Factor IX complex is a sterile freeze-dried concentrate of blood coagulation factors II, VII, IX, and X derived from fresh venous plasma. Factor IX complex, which is used for the treatment of hemophilia B, may also be used for the treatment of bleeding due to deficiencies of factor II, VII, and X. High-purity preparations of factor IX that do not contain clinically effective amounts of factor II, VII, and X are available. A recombinant factor IX preparation is also available.

- **Factor IX complex (coagulation factors, II, VII, IX, X) concentrate**

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 Technical Report Series, No. 840, 1994, Annex 2.

Factor IX complex concentrate is a complementary list preparation and a representative coagulation factor preparation. Various preparations can serve as alternatives.

- **Dosage form**

- Freeze-dried powder

- **Uses**

- Replacement therapy for factor IX deficiency in hemophilia B
- Bleeding due to deficiencies of factors II, VII, or X

- **Contraindication**

- Disseminated intravascular coagulation

- **Precaution**

- Risk of thrombosis (probably less risk with highly purified preparations)

- **Dose**

Hemophilia B, by slow intravenous infusion

- **ADULT** and **CHILD**: According to patient's needs and specific preparation used

Treatment of bleeding due to deficiencies in factor II, VII, or X as well as IX, by slow intravenous infusion

- **ADULT** and **CHILD**: According to patient's needs

- **Adverse effects**

- Allergic reactions including chills and fever

- **Factor VII—recombinant**

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 Technical Report Series, No. 840, 1994, Annex 2.

- **Dosage form**

- Freeze-dried powder

- **Uses**

- Treatment and prophylaxis of hemorrhage in patients with hemophilia A or B with inhibitors to factors VIII or IX, acquired hemophilia, factor VII deficiency, or Glanzmann's thrombasthenia

- **Precaution**

- Risk of thrombosis or disseminated intravascular coagulation

- **Adverse effects**

- Very rarely nausea, thrombotic events (including myocardial infarction and cerebrovascular accident), coagulation disorders, fever, pain, and allergic reactions including rash

- **Factor VIII concentrate**

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 Technical Report Series, No. 840, 1994, Annex 2.

Factor VIII concentrate is a complementary preparation and a representative coagulation factor preparation. Various preparations can serve as alternatives.

- **Dosage form**

- Freeze-dried powder

- **Use**

- Control of hemorrhage in hemophilia A

- **Precaution**

- Intravascular hemolysis after large or frequently repeated doses in patients with blood groups A, B, or AB (less likely with high-potency, highly purified concentrates)

- **Dose**

Hemophilia A, by slow intravenous infusion

- **ADULT** and **CHILD**: According to patient's needs

- **Adverse effects**

- Allergic reactions, including chills and fever

SECTION 12: Cardiovascular medicines

LML strengths and dosage forms are marked in *italic* with an asterisk.

12.1 ANTI-ANGINAL MEDICINES

The three main types of angina are:

- *Stable angina* (angina of effort), where atherosclerosis restricts blood flow in the coronary vessels; attacks are usually caused by exertion and relieved by rest.
- *Unstable angina* (acute coronary insufficiency), which is considered to be an intermediate stage between stable angina and myocardial infarction.
- *Prinzmetal's angina* (variant angina), caused by coronary vasospasm, in which attacks occur at rest.

Management depends on the type of angina and may include drug treatment, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty.

Stable angina

Drugs are used both for the relief of acute pain and for prophylaxis (to reduce the risk of further attacks); they include organic nitrates, beta-adrenoceptor antagonists (beta-blockers), and calcium-channel blockers.

Nitrates

Organic nitrates have a vasodilating effect; they are sometimes used alone, especially in the elderly patients with infrequent symptoms. Tolerance leading to reduced anti-anginal effect is often seen in patients taking prolonged-action nitrate formulations. Evidence suggests that patients should have a “nitrate-free” interval to prevent the development of tolerance. Adverse effects such as flushing, headache, and postural hypotension may limit

nitrate therapy but tolerance to these effects also soon develops. The short-acting sublingual formulation of **glyceryl trinitrate** is used both for prevention of angina before exercise or other stress and for rapid treatment of chest pain. A sublingual tablet of **isosorbide dinitrate** is more stable in storage than glyceryl trinitrate and is useful in patients who require nitrates infrequently; it has a slower onset of action, but effects persist for several hours.

Beta-blockers

Beta-adrenoceptor antagonists (beta-blockers), such as **atenolol**, block beta-adrenergic receptors in the heart and thereby decrease heart rate and myocardial contractility and oxygen consumption, particularly during exercise. Beta-blockers are first-line therapy for patients with effort-induced chronic stable angina; they improve exercise tolerance, relieve symptoms, reduce the severity and frequency of angina attacks, and increase the anginal threshold. Beta-blockers should be withdrawn gradually to avoid precipitating an anginal attack; they should not be used in patients with underlying coronary vasospasm (Prinzmetal's angina).

Beta-blockers may precipitate asthma and should not be used in patients with a history of asthma or bronchospasm. Some, including atenolol, have less effect on beta₂- (bronchial) receptors and are therefore relatively cardioselective. Although the cardioselective beta-blockers have less effect on airway resistance, they are not free of this effect and should be avoided in patients with asthma or bronchospasm; in rare situations where there is no suitable alternative, a cardioselective beta-blocker can be given with extreme caution under specialist supervision.

Beta-blockers should not be given to patients who have incipient ventricular failure, second- or third-degree atrioventricular block, or peripheral vascular disease.

Beta-blockers should be used with caution in diabetes. Beta-blockers can produce hyperglycemia or they can enhance the hypoglycemic effect of insulin and may precipitate hypoglycemia

Calcium-channel blockers

A long-acting dihydropyridine calcium-channel blocker (such as **amlodipine**, usual dose, 5 mg once daily, Section 12.3) can be added to beta-blocker treatment if necessary for the control of moderate stable angina. For those in whom a beta-blocker is inappropriate, **verapamil** may be given as an alternative to treat stable angina. Calcium-channel blockers interfere with the inward movement of calcium ions through the slow channels in heart and vascular smooth muscle cell membranes, leading to relaxation of vascular smooth muscle. Myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed, and coronary or systemic vascular tone may be diminished. Calcium-channel blockers are used to improve exercise tolerance in patients with chronic stable angina due to coronary atherosclerosis or with abnormally small coronary arteries and limited vasodilator reserve.

Calcium-channel blockers can also be used in patients with unstable angina with a vasospastic origin, such as Prinzmetal's angina, and in patients in whom alterations in cardiac tone may influence the angina threshold.

Unstable angina

Unstable angina requires prompt aggressive treatment to prevent progression to myocardial infarction.

Initial treatment is with acetylsalicylic acid to inhibit platelet aggregation, followed by heparin (Section 10.2). Nitrates and beta-blockers are given to relieve ischemia; if beta-blockers are contraindicated, **verapamil** is an alternative, provided left ventricular function is adequate (*see also* Section 12.5).

Prinzmetal's angina

Treatment is similar to that for unstable angina, except that a calcium-channel blocker is used instead of a beta-blocker.

- **Atenolol**

Atenolol is a representative beta-adrenoceptor antagonist (beta-blocker). Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 25 mg, 50 mg, and 100 mg

- **Uses**

- Angina and myocardial infarction (*see also* Section 12.5)
- Arrhythmias (Section 12.2)
- Hypertension (Section 12.3)
- Migraine prophylaxis (Section 7.2)

- **Contraindications**

- History of asthma or bronchospasm (unless no alternative, in which case use with extreme caution and under specialist supervision)
- Uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- and third-degree atrioventricular block, cardiogenic shock
- Metabolic acidosis
- Severe peripheral arterial disease
- Pheochromocytoma (unless used with an alpha-blocker)

- **Precautions**

- Avoid abrupt withdrawal especially in ischemic heart disease
- History of obstructive airway disease (use with caution and monitor lung function) (*see also* Contraindications above)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- First-degree atrioventricular block
- Portal hypertension (liver function deteriorates)

- Renal impairment (reduce dose): Appendix D
- Diabetes mellitus (small decrease in glucose tolerance, which can mask symptoms of hypoglycemia)
- History of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine [adrenaline])
- Myasthenia gravis
- **Interactions:** Appendix A

○ **Dose**

Angina, by mouth

- **ADULT:** 50 mg once daily, increased if necessary to 50 mg twice daily or 100 mg once daily

Unstable angina and acute myocardial infarction (early intervention within 12 hours), by intravenous injection over 5 minutes

- **ADULT:** 5 mg, then *by mouth*, 50 mg after 15 minutes, followed by 50 mg after 12 hours, then 100 mg daily

○ **Adverse effects**

- Gastrointestinal disturbances including nausea, vomiting, diarrhea, constipation, and abdominal cramp
- Fatigue
- Cold hands and feet
- Exacerbation of intermittent claudication and Raynaud's phenomenon
- Bronchospasm
- Bradycardia, heart failure, conduction disorders, hypotension
- Sleep disturbances including nightmares
- Depression, confusion
- Hypoglycemia or hyperglycemia
- Exacerbation of psoriasis

- Rash, dry eyes, and oculomucocutaneous syndrome (reversible on withdrawal) rarely reported

- **Glyceryl trinitrate / nitroglycerine**

- **Dosage form**

- Sublingual-oral tablets: 0.4 mg and 0.5 mg
 - Injection: 1 mg/ml in 5 ml ampoule, 5 mg/ml
 - Transdermal patch: 5 mg/patch

Note: Glyceryl trinitrate tablets are unstable. They should therefore be dispensed in glass or stainless-steel containers, and closed with a foil-lined cap that contains no wadding. No more than 100 tablets should be dispensed at one time, and any unused tablets should be discarded 8 weeks after opening the container.

- **Uses**

- Prophylaxis and treatment of angina

- **Contraindications**

- Hypersensitivity to nitrates
 - Hypotension
 - Hypovolemia
 - Hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis
 - Marked anemia
 - Head trauma
 - Cerebral hemorrhage
 - Angle-closure glaucoma

- **Precautions**

- Severe hepatic impairment: Appendix E

- Renal impairment: Appendix D
- Hypothyroidism
- Malnutrition
- Hypothermia
- Recent history of myocardial infarction
- **Interactions:** Appendix A

- **Dose**

Angina (acute attack), sublingually

- **ADULT:** 0.5–1 mg, repeated as required

- **Adverse effects**

- Throbbing headache
- Flushing
- Dizziness, postural hypotension
- Tachycardia
- Paradoxical bradycardia also reported

- **Isosorbide**

Isosorbide mononitrate and dinitrate is a representative nitrate vasodilator. Various drugs can serve as alternatives.

- **Dosage form**

- Sublingual-oral tablets: 5 mg, 10 mg, and 20 mg (as dinitrate)
- Tablets: 40 mg, 60 mg, and 120 mg (as mononitrate)

- **Uses**

- Prophylaxis and treatment of angina
- Heart failure (Section 12.4)

- **Contraindications**

- Hypersensitivity to nitrates
 - Hypotension
 - Hypovolemia
 - Hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis
 - Marked anemia
 - Head trauma
 - Cerebral hemorrhage
 - Angle-closure glaucoma
- **Precautions**
 - Severe hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Hypothyroidism
 - Malnutrition
 - Hypothermia
 - Recent history of myocardial infarction
 - **Interactions:** Appendix A
 - **Dose**

Angina (acute attack), sublingually

- **ADULT:** 2.5–10 mg, repeated as required

Angina prophylaxis, by mouth

- **ADULT:** 20–240 mg daily in divided doses

Tolerance: Patients taking isosorbide dinitrate for the long-term management of angina may often develop tolerance to the anti-anginal 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.

- **Adverse effects**

- Throbbing headache
- Flushing
- Dizziness, postural hypotension
- Tachycardia
- Paradoxical bradycardia also reported

- **Propranolol**

Propranolol is a representative beta-adrenoceptor antagonist. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 10 mg, 20 mg, and 40 mg

- **Uses**

- Angina, arrhythmias, hypertension, anxiety, prophylaxis after myocardial infarction, phaeochromocytoma (only with an alpha-blocker)
- Prophylaxis of migraine (Section 7.2)

- **Contraindications**

- See Section 7.2.

- **Precautions**

- See Section 7.2.

- **Dose**

Angina, by mouth

- Initially 40 mg 2–3 times daily; maintenance 120–240 mg daily

Arrhythmias, hypertrophic cardiomyopathy, anxiety tachycardia, and thyrotoxicosis (adjunct)

- 10–40 mg 3–4 times daily

Anxiety with symptoms such as palpitation, sweating, tremor, by mouth

- 40 mg once daily, increased to 40 mg 3 times daily if necessary

Prophylaxis of variceal bleeding in portal hypertension, by mouth

- Initially 40 mg twice daily, increased to 80 mg twice daily according to heart rate; maximum 160 mg twice daily

Phaeochromocytoma (only with an alpha-blocker), by mouth

- 60 mg daily for 3 days before surgery or 30 mg daily in patients unsuitable for surgery

Prophylaxis after myocardial infarction

- 40 mg 4 times daily for 2–3 days, then 80 mg twice daily, beginning 5–21 days after infarction

- **Adverse effects**

- See Section 7.2.

- **Metoprolol**

- **Dosage form**

- Injection solution: 1 mg/ml in 5 ml ampoule
- Tablets: 50 mg and 100 mg

- **Uses**

- Angina

- Early intervention within 12 hours of infarction
- Hypertension (Section 12.3)
- Migraine prophylaxis (Section 7.2)
- Arrhythmias, to control arrhythmias developing during anesthesia (Section 12.2)

○ **Contraindications**

- *See under* Propranolol hydrochloride.

○ **Precautions**

- *See under* Propranolol hydrochloride.
- Hepatic impairment: Appendix E
- Breast-feeding: Appendix C
- Pregnancy: Appendix B

○ **Dose**

Angina, by mouth

- 50–100 mg 2–3 times daily

Early intervention within 12 hours of infarction, by intravenous injection

- 5 mg every 2 minutes to a maximum of 15 mg, followed after 15 minutes by 50 mg *by mouth* every 6 hours for 48 hours; maintenance 200 mg daily in divided doses

Note: Excessive bradycardia can be countered with intravenous injection of atropine sulfate 0.6–2.4 mg in divided doses of 600 micrograms.

○ **Adverse effects**

- *See under* Propranolol hydrochloride.

- **Verapamil**

- **Dosage form**

- Tablets: 40 mg and 80 mg, and 240 mg* (as hydrochloride)
 - Injection: 2.5 mg/ml in 2 ml ampoule

- **Uses**

- Angina, including stable, unstable, and Prinzmetal's
 - Arrhythmias (Section 12.2)
 - Migraine prophylaxis (Section 7.2)

- **Contraindications**

- 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
 - Porphyria

- **Precautions**

- First-degree atrioventricular block
 - Acute phase of myocardial infarction (avoid if bradycardia, hypotension, or left ventricular failure present)
 - Hepatic impairment: Appendix E
 - Children (specialist advice only)
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Avoid grapefruit juice (may affect metabolism)
 - **Interactions:** Appendix A

- **Dose**

Angina, by mouth

- **ADULT:** 80–120 mg 3 times daily (120 mg 3 times daily usually required in Prinzmetal's angina)

- **Adverse effects**

- Constipation
- Less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, and ankle edema
- Rarely allergic reactions including pruritus, urticaria, angioedema, and erythema multiforme (Stevens-Johnson syndrome)
- Myalgia, arthralgia, paresthesia, erythromelalgia
- Increased prolactin concentration
- Gynecomastia and gingival hyperplasia on long-term treatment
- Hypotension, heart failure, bradycardia, heart block, and asystole (due to negative inotropic effect) with high doses.

12.2 ANTI-ARRHYTHMIC MEDICINES

Treatment of arrhythmias requires precise diagnosis of the type of arrhythmia, for which electrocardiography (ECG) is essential; underlying causes such as heart failure require appropriate treatment.

Anti-arrhythmics must be used cautiously since most drugs that are effective in treating arrhythmias can provoke them in some circumstances; this arrhythmogenic effect is often enhanced by hypokalemia. When anti-arrhythmic drugs are used in combination, their cumulative negative inotropic effects may be significant, particularly if myocardial function is impaired.

Atrial fibrillation

The increased ventricular rate in atrial fibrillation can be controlled with a beta-adrenoceptor antagonist (beta-blocker), such as **atenolol**, or a calcium-channel blocker, such as **verapamil**. **Digoxin**, a cardiac glycoside, slows the ventricular response and is particularly appropriate if atrial fibrillation is accompanied by congestive heart failure. Intravenous digoxin is rarely of value for rapid control of the ventricular rate because response may take many hours. If adequate control at rest or during exercise cannot be achieved readily, verapamil may be introduced with digoxin, but it should be used with caution if ventricular function is impaired. Anticoagulants are indicated especially in valvular or myocardial disease, and in the elderly. Warfarin is preferred to acetylsalicylic acid in preventing emboli. If atrial fibrillation began within the previous 48 hours, and there does not appear to be a danger of thromboembolism, anti-arrhythmic drugs, such as **procainamide** or **quinidine**, may be used to terminate the fibrillation or to maintain sinus rhythm after cardioversion.

Atrial flutter

Digoxin will sometimes slow the ventricular response. Reversion to sinus rhythm is best achieved by direct current electrical shock. If the arrhythmia is long-standing, treatment with an anticoagulant, such as warfarin, should be considered before cardioversion to prevent emboli. Intravenous **verapamil** reduces ventricular fibrillation during paroxysmal (sudden onset and intermittent) attacks of atrial flutter. An initial intravenous dose may be followed by oral treatment; hypotension may occur with high doses. Verapamil should not be used for tachyarrhythmias where the QRS complex is wide, unless a supraventricular origin has been established beyond doubt. If the flutter cannot be restored to sinus rhythm, an anti-arrhythmic, such as quinidine, can be used.

Paroxysmal supraventricular tachycardia

In most patients, this remits spontaneously or can revert to sinus rhythm by reflex vagal stimulation. Failing this, intravenous injection of a beta-blocker or verapamil may be effective. Verapamil and a beta-blocker should **NEVER** be administered concomitantly because of the risk of hypotension and asystole.

Ventricular tachycardia

Very rapid ventricular fibrillation causes profound circulatory collapse and must be treated immediately with direct current shock. In more stable patients, intravenous **lidocaine** or **procainamide** may be used. After sinus rhythm is restored, drug therapy to prevent recurrence of ventricular tachycardia should be considered; a beta-adrenoceptor antagonist (beta-blocker) or **verapamil** may be effective.

Bradyarrhythmias

Sinus bradycardia (less than 50 beats/min) associated with acute myocardial infarction may be treated with atropine (Section 1.3). Temporary pacing may be required in unresponsive patients. Drugs are of limited value for increasing the sinus rate long term in the presence of intrinsic sinus node disease, and permanent pacing is usually required.

Cardiac arrest

In cardiac arrest, **epinephrine** (adrenaline) is given by intravenous injection in a dose of 1 mg (10 ml of 1:10,000 solution) as part of the procedure for cardiopulmonary resuscitation.

- **Atenolol**

Atenolol is a representative beta-adrenoceptor antagonist (beta-blocker). Various drugs can serve as alternatives.

- **Dosage form**

- Tablets: 25 mg, 50 mg, and 100 mg

- **Uses**

- Arrhythmias
- Angina and myocardial infarction (Section 12.1)

- Hypertension (Section 12.3)
- Migraine prophylaxis (Section 7.2)

- **Contraindications**

- See Section 12.1.

- **Precautions**

- See Section 12.1.

- **Dose**

Arrhythmias, by mouth

- **ADULT:** 50 mg once daily, increased if necessary to 50 mg twice daily or 100 mg once daily

- **Adverse effects**

- See Section 12.1.

- **Digoxin**

- **Dosage form**

- Tablets: 0.125 mg* and 0.25 mg
- Oral drops: 0.05 mg/mL*
- Injection solution: 0.1 mg/mL* and 0.25 mg/ml in 2 ml ampoule

- **Uses**

- Supraventricular arrhythmias, particularly atrial fibrillation
- Heart failure (Section 12.4)

- **Contraindications**

- Hypertrophic obstructive cardiomyopathy (unless also atrial fibrillation and heart failure)

- Wolff-Parkinson-White syndrome or other accessory pathway, particularly if accompanied by atrial fibrillation
 - Ventricular tachycardia or fibrillation
 - Intermittent complete heart block
 - Second-degree atrioventricular block
- **Precautions**
- Recent myocardial infarction
 - Sick sinus syndrome
 - Severe pulmonary disease
 - Thyroid disease
 - Elderly (reduce dose)
 - Renal impairment: Appendix D
 - Avoid hypokalemia
 - Avoid rapid intravenous administration (nausea and increased risk of arrhythmias)
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A

○ **Dose**

Atrial fibrillation, by mouth

- **ADULT:** 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, 125–250 micrograms daily (lower dose more appropriate in the elderly)

Emergency control of atrial fibrillation, by intravenous infusion over at least 2 hours

- **ADULT:** 0.75–1 mg

Note: Infusion dose may need to be reduced if digoxin or other cardiac glycoside has been given in previous 2 weeks.

- **Adverse effects**

- Usually only associated with high doses
- Gastrointestinal disturbances including anorexia, nausea, vomiting, diarrhea, and abdominal pain
- Visual disturbances, headache, fatigue, drowsiness, confusion, dizziness, delirium, hallucinations, depression
- Arrhythmias, heart block
- Rarely rash and intestinal ischemia
- Gynecomastia on long-term use
- Thrombocytopenia reported

- **Epinephrine (adrenaline)**

- **Dosage form**

- Injection: 0.1% in 1 ml ampoule

- **Uses**

- Cardiac arrest
- Anaphylaxis (Section 3)
- Asthma (Section 25.1)

- **Precautions**

- Heart disease, hypertension, arrhythmias, cerebrovascular disease
- Hyperthyroidism, diabetes mellitus
- Angle-closure glaucoma

- Second stage of labor
- **Interactions:** Appendix A

○ **Dose**

Caution: Different dilutions of epinephrine injection are used for different routes of administration.

Cardiac arrest, by intravenous injection through a central line using epinephrine injection 1:10,000 (100 micrograms/ml)

- **ADULT:** 1 mg (10 ml), repeated at 3-minute intervals if necessary

Note: If a central line is not in place, the same dose can be given via a peripheral vein, then flushed through with at least 20 ml sodium chloride, 0.9% (to expedite entry into the circulation).

○ **Adverse effects**

- Anxiety, tremor, tachycardia, headache, cold extremities
- Nausea, vomiting, sweating, weakness, dizziness, and hyperglycemia also reported
- In overdosage: arrhythmias, cerebral hemorrhage, and pulmonary edema

● **Lidocaine**

○ **Dosage form**

- Injection: 20 mg (as hydrochloride)/ml in 5 ml ampoule

○ **Uses**

- Ventricular arrhythmias (especially after myocardial infarction)
- Local anesthesia (Section 1.2)

○ **Contraindications**

- Sinoatrial disorder
 - Any grade of atrioventricular block or any other type of conduction disturbance
 - Severe myocardial depression
 - Acute porphyria or hypovolemia
- **Precautions**
- Lower dosage in congestive heart failure and following cardiac surgery
 - Bradycardia
 - Hepatic impairment: Appendix E
 - Severe respiratory depression
 - Elderly
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A
- **Dose**

Ventricular arrhythmias, by intravenous injection

- **ADULT:** Loading dose of 50–100 mg (or 1–1.5 mg/kg) at a rate of 25–50 mg/min, followed immediately *by intravenous infusion* of 1–4 mg/min, with ECG monitoring of all patients (reduce infusion dose if required for longer than 24 hours)

Important: Following intravenous injection, lidocaine has a short duration of action (15–20 minutes). If the intravenous infusion cannot be given immediately, the initial intravenous injection of 50–100 mg can be repeated if necessary once or twice at intervals of not less than 10 minutes.

- **Adverse effects**

- Dizziness, paresthesia, drowsiness, confusion, apnea, respiratory depression, coma, seizures and convulsions, hypotension
- Arrhythmias, heart block, cardiovascular collapse, bradycardia (may lead to cardiac arrest)
- Nystagmus (often an early sign of lidocaine overdose)
- Hypersensitivity reactions also reported

- **Metoprolol**

- **Dosage form**

- Injection solution: 1 mg/ml in 5 ml ampoule
- Tablets: 50 mg and 100 mg

- **Uses**

- Arrhythmias, control arrhythmias, within 12 hours of infarction
- Hypertension (Section 12.3)
- Angina (Section 12.1)
- Migraine prophylaxis (Section 7.2)

- **Contraindications**

- *See under* Propranolol hydrochloride.

- **Precautions**

- *See under* Propranolol hydrochloride.
- Hepatic impairment: Appendix E
- Breast-feeding: Appendix C
- Pregnancy: Appendix B

- **Dose**

Arrhythmias, by mouth

- Usually 50 mg 2–3 times daily; up to 300 mg daily in divided doses if necessary

Arrhythmias, by intravenous injection

- Up to 5 mg at rate 1–2 mg/min, repeated after 5 minutes if necessary, total dose 10–15 mg

Note: Excessive bradycardia can be countered with intravenous injection of atropine sulfate 0.6–2.4 mg in divided doses of 600 micrograms.

In surgery, by slow intravenous injection

- 2–4 mg at induction or to control arrhythmias developing during anesthesia; 2 mg doses may be repeated to a maximum of 10 mg

Early intervention within 12 hours of infarction, by intravenous injection

- 5 mg every 2 minutes to a maximum of 15 mg, followed after 15 minutes by 50 mg *by mouth* every 6 hours for 48 hours; maintenance 200 mg daily in divided doses

- **Adverse effects**

- See under Propranolol hydrochloride.

□ **Procainamide**

Procainamide is a representative anti-arrhythmic drug. Various drugs can serve as alternatives.

- **Dosage form**

- Injection: 100 mg (hydrochloride)/ml in 10 ml ampoule
- Tablet: 250 mg

- **Uses**

- Severe ventricular arrhythmias, especially those resistant to lidocaine or those appearing after myocardial infarction
 - Atrial tachycardia, atrial fibrillation
 - Maintenance of sinus rhythm after cardioversion of atrial fibrillation
- **Contraindications**
 - Torsades de pointes, systemic lupus erythematosus, heart block, heart failure, hypotension
- **Precautions**
 - Elderly
 - Renal impairment: Appendix D
 - Hepatic impairment: Appendix E
 - Asthma
 - Myasthenia gravis
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C, use only under specialist supervision
 - **Interactions:** Appendix A
- **Dose**

Ventricular arrhythmias, by mouth

- **ADULT:** Up to 50 mg/kg daily in divided doses every 3–6 hours, preferably controlled by monitoring plasma procainamide concentration (therapeutic concentration usually within the range of 3–10 micrograms/ml)

Ventricular arrhythmias, by slow intravenous injection

- **ADULT:** 100 mg at a rate not exceeding 50 mg/min, with ECG monitoring; may be repeated at 5-minute intervals until arrhythmia controlled; maximum 1g

Ventricular arrhythmias, by intravenous infusion

- **ADULT:** 500–600 mg over 25–30 minutes, with ECG monitoring, followed by a maintenance dose of 2–6 mg/min; if further anti-arrhythmic treatment is required, allow an interval of 3–4 hours after infusion before giving further drug therapy by mouth

Atrial arrhythmias

- Higher doses may be required.

- **Adverse effects**

- Nausea, vomiting, diarrhea, anorexia, rash, pruritus, urticaria, flushing, fever, myocardial depression, heart failure, angioedema, depression, dizziness, psychosis
- Blood disorders including leukopenia, hemolytic anemia, and agranulocytosis after prolonged treatment
- Lupus erythematosus–like syndrome
- High plasma procainamide concentration may impair cardiac conduction

- **Verapamil**

- **Dosage form**

- Tablet: 40 mg, 80 mg, and 240 mg (hydrochloride)
- Injection: 2.5 mg (hydrochloride)/ml in 2 ml ampoule

- **Uses**

- Supraventricular arrhythmias
- Angina (Section 12.1)
- Migraine prophylaxis (Section 7.2)

- **Contraindications**

- See Section 12.1.

- **Precautions**

- See Section 12.1.
- **Verapamil and beta-blockers:** Both verapamil and beta-blockers have cardiodepressant activity, and their use together may lead to bradycardia, heart block, and left ventricular failure, particularly in patients with myocardial insufficiency. Treatment with beta-blockers should be discontinued at least 24 hours before intravenous administration of verapamil.

- **Dose**

Supraventricular arrhythmias, by mouth

- **ADULT:** 40–120 mg 3 times daily

Supraventricular arrhythmias, by intravenous injection

- **ADULT:** 5–10 mg over 2 minutes, preferably with ECG monitoring
- **ELDERLY:** 5–10 mg over 3 minutes
- In paroxysmal tachyarrhythmias, a further 5 mg may be given after 5–10 minutes if required.

- **Adverse effects**

- See Section 12.1.

12.3 ANTIHYPERTENSIVE MEDICINES

Management of hypertension

Treatment of hypertension should be integrated into a program to manage all factors that increase the risk of cardiovascular events (such as stroke and myocardial infarction); the overall risk of cardiovascular disease should be assessed for all patients with hypertension. Treatment is often life-long.

Hypertension was formerly classified as mild, moderate, or severe, but a grading system is now preferred. Grade 1 hypertension is defined as 140–159 mmHg systolic blood pressure and 90–99 mmHg diastolic blood pressure; Grade 2 hypertension is defined as 160–179 mmHg systolic and 100–109 mmHg diastolic; and Grade 3 hypertension is defined as more than 180 mmHg systolic and more than 110 mmHg diastolic. The aim of treatment in most patients is an optimal target systolic blood pressure of less than 140 mmHg and a diastolic blood pressure of less than 85 mmHg. For patients with diabetes, the aim is a systolic blood pressure of less than 130 mmHg and a diastolic blood pressure of less than 80 mmHg. In some patients, these targets are not possible despite adequate treatment; however, any decrease in blood pressure reduces the risk of cardiovascular disease.

The objective of lowering raised blood pressure is to decrease the risk of stroke, coronary events, heart failure, and renal impairment. Patients should be given advice on lifestyle changes to reduce blood pressure or cardiovascular risk; these include smoking cessation, weight reduction, reduction of excessive intake of alcohol, reduction of dietary salt, reduction of total and saturated fat, increasing exercise, and increasing fruit and vegetable intake. These measures may not be sufficient to reduce blood pressure (especially moderate and severe hypertension) below the suggested target; in these cases antihypertensive drugs may be needed.

Drug treatment of hypertension

Response to drug treatment for hypertension may be affected by the patient's age and ethnic background.

Antihypertensive treatment should be selected according to the individual's clinical needs, any conditions that render certain drugs less suitable for the individual, and the availability and cost of drugs.

There are three classes of antihypertensive drugs used for the treatment of hypertension:

- Thiazide diuretics
- Beta-adrenoceptor antagonists (beta-blockers)
- ACE inhibitors

Thiazide diuretics, such as **hydrochlorothiazide**, should usually be considered for antihypertensive therapy; they are particularly indicated in the elderly. They have few adverse effects in low doses, but in large doses they may cause a variety of unwanted metabolic effects (principally, potassium depletion), reduced glucose tolerance, ventricular ectopic beats, and impotence; they should be avoided in gout. These effects can be reduced by keeping the dose as low as possible; higher doses do not produce an increased reduction in blood pressure. Thiazides are inexpensive and, when used in combination, can enhance the effectiveness of many other classes of antihypertensive drug.

Beta-adrenoceptor antagonists (beta-blockers), such as **atenolol**, are effective in all grades of hypertension, and are particularly useful in angina and following myocardial infarction; they should be avoided in asthma, chronic obstructive pulmonary disease, and heart block. Beta-blockers, especially in combination with a thiazide, are best avoided in patients with diabetes or those at high risk of developing diabetes.

Angiotensin converting enzyme (ACE) inhibitors, such as **enalapril**, are effective and well tolerated by most patients. They can be used in heart failure (see Section 12.4), left ventricular dysfunction, and diabetic nephropathy, but should be avoided in renovascular disease and in pregnancy. The most common adverse effect is a dry persistent cough.

Dihydropyridine calcium-channel blockers, such as **amlodipine**, are useful for isolated systolic hypertension, in populations unresponsive to other antihypertensives (for example, Africans).

Drugs acting on the central nervous system are also effective antihypertensive drugs. In particular, **methyldopa** is effective in the treatment of hypertension in pregnancy.

A single antihypertensive drug is often not adequate and other antihypertensive drugs are usually added in a stepwise manner until blood pressure is controlled.

Hypertensive emergencies

In situations where immediate reduction of blood pressure is essential and treatment by mouth is not possible, intravenous infusion of **sodium nitroprusside** is effective.

However, over-rapid reduction in blood pressure is hazardous and can lead to reduced organ perfusion and cerebral infarction.

Pregnancy

In pregnancy, hypertension is defined as a sustained diastolic blood pressure of 90 mmHg or more. Drug therapy for chronic hypertension during pregnancy remains controversial. If diastolic blood pressure is greater than 95 mmHg, **methyldopa** is the safest drug.

Beta-blockers should be used with caution in pregnancy, since they can restrict fetal growth if used for an extended period; intrauterine growth restriction is minimized if use is limited to the third trimester. **ACE inhibitors are contraindicated in pregnancy** since they may damage fetal and neonatal blood pressure control and renal function. Women who are taking these drugs and become pregnant should have their antihypertensive therapy changed immediately.

Pre-eclampsia and eclampsia

If pre-eclampsia or severe hypertension occurs after week 36 of pregnancy, delivery is the treatment of choice. For acute severe hypertension in pre-eclampsia or eclampsia,

intravenous **hydralazine** can be used. **Magnesium sulfate** is the treatment of choice to prevent eclamptic convulsions in eclampsia and severe pre-eclampsia.

- **Amlodipine**

Amlodipine is a representative dihydropyridine calcium-channel blocker. Various drugs can serve as alternatives.

- **Dosage form**

- Tablets: 5 mg and 10 mg

Note: Tablets from different suppliers may contain different salts (e.g., amlodipine besilate, amlodipine maleate, amlodipine mesilate) but the strength is expressed in terms of amlodipine (base); tablets containing different salts are considered interchangeable.

- **Uses**

- Hypertension
- Angina (*see also* Section 12.1)

- **Contraindications**

- Cardiogenic shock
- Unstable angina
- Significant aortic stenosis

- **Precautions**

- Hepatic impairment: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Dose**

Angina, by mouth

- **ADULT:** Initially 5 mg once daily, increased if necessary; maximum 10 mg once daily

Hypertension, by mouth

- **ADULT:** Initially 5 mg once daily, increased if necessary; maximum 10 mg once daily

- **Adverse effects**

- Abdominal pain, nausea
- Palpitation, flushing, edema
- Headache, dizziness, sleep disturbances, fatigue
- Less commonly gastrointestinal disturbances, dry mouth, taste disturbances, hypotension, syncope, chest pain, dyspnea, rhinitis, mood changes, tremor, paresthesia, increased sweating, urinary disturbances, impotence, gynecomastia, weight changes, myalgia, arthralgia, muscle cramps, visual disturbances, tinnitus, pruritus, rash (including isolated reports of erythema multiforme), alopecia, purpura, and skin discoloration
- Very rarely gastritis, pancreatitis, hepatitis, jaundice, cholestasis, gingival hyperplasia, myocardial infarction, arrhythmias, vasculitis, coughing, hyperglycemia, thrombocytopenia, peripheral neuropathy, angioedema, and urticaria

- **Atenolol**

Atenolol is a representative beta-adrenoceptor antagonist (beta-blocker). Various drugs can serve as alternatives.

- **Dosage form**

- Tablets: 25 mg, 50 mg, and 100 mg

- **Uses**
 - Hypertension
 - Angina (Section 12.1)
 - Arrhythmias (Section 12.2)
 - Migraine prophylaxis (Section 7.2)

- **Contraindications**
 - See Section 12.1.

- **Precautions**
 - See Section 12.1.

- **Dose**

Hypertension, by mouth

- **ADULT:** 50 mg once daily (higher doses rarely necessary)

- **Adverse effects**
 - See Section 12.1.

- **Captopril**

- **Dosage form**
 - Tablets: 25 mg and 50 mg

- **Uses**
 - Mild-to-moderate essential hypertension alone or with thiazide therapy and severe hypertension resistant to other treatment
 - Congestive heart failure with left ventricular dysfunction (adjunct)
 - Following myocardial infarction; see Dose.
 - Diabetic nephropathy (microalbuminuria greater than 30 mg/day) in type 1 diabetes

- **Contraindications**

- ACE inhibitors are contraindicated in patients with hypersensitivity to ACE inhibitors (including angioedema).

- **Precautions**

- ACE inhibitors need to be initiated with care in patients receiving diuretics (important: *see* Concomitant diuretics, below).
- First doses can cause hypotension, especially in patients taking high doses of diuretics, on a low-sodium diet, on dialysis, dehydrated, or with heart failure. They should also be used with caution in peripheral vascular disease or generalized atherosclerosis owing to risk of clinically silent renovascular disease; for use in preexisting renovascular disease, *see* Renal effects, above.
- The risk of agranulocytosis is possibly increased in collagen vascular disease (blood counts recommended).
- ACE inhibitors should be used with care in patients with severe or symptomatic aortic stenosis (risk of hypotension) and in hypertrophic cardiomyopathy. They should also be used with care (or avoided) in those with a history of idiopathic or hereditary angioedema.
- If jaundice or marked elevations of hepatic enzymes occur during treatment, then the ACE inhibitor should be discontinued—risk of hepatic necrosis (*see also* Hepatic impairment, below).
- **Interactions:** Appendix A (ACE inhibitors)
- Hepatic impairment: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix E

Anaphylactoid reactions: To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes

and during low-density lipoprotein apheresis with dextran sulfate; they should also be withheld before desensitization with wasp or bee venom.

Concomitant diuretics: ACE inhibitors can cause a very rapid fall in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. If the dose of diuretic is greater than 80 mg furosemide or equivalent, the ACE inhibitor should be initiated under close supervision and in some patients the diuretic dose may need to be reduced or the diuretic discontinued at least 24 hours beforehand (may not be possible in heart failure—risk of pulmonary edema). If high-dose diuretic therapy cannot be stopped, close observation is recommended after administration of the first dose of ACE inhibitor, for at least 2 hours or until the blood pressure has stabilized.

- **Dose**

Hypertension

- Used alone, initially 12.5 mg twice daily
- If used in addition to diuretic (*see notes above*), or in elderly, initially 6.25 mg twice daily (first dose at bedtime); usual maintenance dose 25 mg twice daily; maximum 50 mg twice daily (rarely 3 times daily in severe hypertension)

Heart failure (adjunct)

- Initially 6.25–12.5 mg 2–3 times daily under close medical supervision (*see notes above*), increased gradually at intervals of at least 2 weeks up to maximum 150 mg daily in divided doses if tolerated

Diabetic nephropathy

- 75–100 mg daily in divided doses; if further blood pressure reduction required, other antihypertensives may be used in conjunction with captopril
- In severe renal impairment, initially 12.5 mg twice daily (if concomitant diuretic therapy required, a loop diuretic rather than thiazide should be chosen)

Prophylaxis after infarction in clinically stable patients with asymptomatic or symptomatic left ventricular dysfunction (radionuclide ventriculography or echocardiography undertaken before initiation)

- Initially 6.25 mg, starting as early as 3 days after infarction, then increased over several weeks to 150 mg daily (if tolerated) in divided doses

○ **Adverse effects**

- ACE inhibitors can cause profound hypotension (see Precautions) and renal impairment (see Renal effects, above), and a persistent dry cough.
- They can also cause angioedema (onset may be delayed; higher incidence reported in Afro-Caribbean patients), rash (which may be associated with pruritus and urticaria), pancreatitis, and upper respiratory tract symptoms such as sinusitis, rhinitis, and sore throat.
- Gastrointestinal effects reported with ACE inhibitors include nausea, vomiting, dyspepsia, diarrhea, constipation, and abdominal pain.
- Altered liver function tests, cholestatic jaundice, hepatitis, fulminant hepatic necrosis, and hepatic failure have been reported—discontinue if marked elevation of hepatic enzymes or jaundice.
- Hyperkalemia, hypoglycemia, and blood disorders including thrombocytopenia, leukopenia, neutropenia, and hemolytic anemia have also been reported.
- Other reported side effects include headache, dizziness, fatigue, malaise, taste disturbance, paresthesia, bronchospasm, fever, serositis, vasculitis,

myalgia, arthralgia, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leukocytosis, and photosensitivity.

- Tachycardia, serum sickness, weight loss, stomatitis, maculopapular rash, photosensitivity, flushing, and acidosis.

- **Enalapril**

Enalapril is a representative ACE inhibitor. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 5 mg, 10 mg, and 20 mg

- **Uses**

- Hypertension
 - Heart failure (Section 12.4)

- **Contraindications**

- Hypersensitivity to ACE inhibitors (including angioedema)
 - Renovascular disease
 - Pregnancy: Appendix B

- **Precautions**

- Concomitant use of diuretics (*see note below*)
 - 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)
 - Monitor renal function before and during treatment
 - Renal impairment (reduce dose): Appendix D
 - Hepatic impairment: Appendix E

- Possibly increased risk of agranulocytosis in collagen vascular disease
- History of idiopathic or hereditary angioedema (use with care or avoid)
- Breast-feeding: Appendix C
- **Interactions:** Appendix A
- **Use with diuretics:** Because of the risk of very rapid falls in blood pressure in volume-depleted patients, treatment should be initiated with very low doses. High-dose diuretic therapy (for example, with furosemide at doses greater than 80 mg daily) should be discontinued, or the dose significantly reduced, at least 24 hours before starting enalapril (this may not be possible in heart failure due to the risk of pulmonary edema). If high-dose diuretic therapy cannot be stopped, medical supervision is advised for at least 2 hours after administration or until blood pressure is stable.
- **Anaphylactoid reactions:** Avoid enalapril during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; also withhold before desensitization with wasp or bee venom.

○ Dose

Hypertension, by mouth

- **ADULT:** Initially 5 mg once daily (lower if used in addition to a diuretic or in renal impairment); increased if necessary; usual maintenance dose, 20 mg once daily; maximum 40 mg, once daily.

○ Adverse effects

- Dizziness, headache
- Less commonly nausea, diarrhea, hypotension (severe in rare cases), dry cough, fatigue, asthenia, muscle cramps, rash, and renal impairment
- Rarely vomiting, dyspepsia, abdominal pain, constipation, peptic ulcer, glossitis, stomatitis, ileus, anorexia, pancreatitis, liver damage, chest pain,

palpitations, arrhythmias, Raynaud's syndrome, angioedema, bronchospasm, rhinorrhea, dry mouth, sore throat, pulmonary infiltrates, paresthesia, vertigo, nervousness, depression, confusion, drowsiness, insomnia, dream abnormalities, pruritus, urticaria, alopecia, flushing, impotence, gynecomastia, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus, taste disturbances, tinnitus, and blurred vision

- Electrolyte disturbances and hypersensitivity-like reactions (including fever, myalgia, arthralgia, eosinophilia, and photosensitivity) also reported

- **Hydralazine**

- **Dosage form**

- Injection: 20 mg/ml in 2 ml ampoule (as hydrochloride)
 - Tablets: 25 mg and 50 mg

- **Uses**

- In combination therapy in moderate-to-severe hypertension, hypertensive crises
 - Hypertension associated with pregnancy (including pre-eclampsia or eclampsia)
 - Heart failure (Section 12.4)

- **Contraindications**

- Idiopathic systemic lupus erythematosus
 - Severe tachycardia
 - High-output heart failure
 - Myocardial insufficiency due to mechanical obstruction
 - Cor pulmonale
 - Dissecting aortic aneurysm
 - Porphyrria

- **Precautions**

- Hepatic impairment: Appendix E
- Renal impairment (reduce dose): Appendix D
- Coronary artery disease (may provoke angina; avoid after myocardial infarction until stabilized)
- Cerebrovascular disease
- Pregnancy: Appendix B
- Breast-feeding: Appendix C.
- Occasionally over-rapid blood pressure reduction even with low parenteral doses
- **Interactions:** Appendix A

- **Dose**

Hypertension, by mouth

- **ADULT:** 25 mg twice daily, increased if necessary to maximum, 50 mg twice daily

Hypertensive crisis (including during pregnancy), by slow intravenous injection

- **ADULT:** 5–10 mg diluted with 10 ml sodium chloride, 0.9%; if necessary may be repeated after 20–30 minutes (*see also* Precautions)

Hypertensive crisis (including during pregnancy), by intravenous infusion

- **ADULT:** Initially 200–300 micrograms/min; usual maintenance dose 50–150 micrograms/min

Hypertensive crisis (including during pregnancy), by intramuscular injection

- **ADULT:** 12.5 mg every 2 hours, repeated as necessary

Reconstitution and administration: According to manufacturer's directions

- **Adverse effects**

- Tachycardia, palpitations, postural hypotension
- Fluid retention
- Gastrointestinal disturbances including anorexia, nausea, vomiting, diarrhea, and rarely constipation
- Dizziness, flushing, headache
- Abnormal liver function, jaundice
- Systemic lupus erythematosus–like syndrome, particularly in women and slow acetylators
- Nasal congestion, agitation, anxiety, polyneuritis, peripheral neuritis, rash, fever, paresthesia, arthralgia, myalgia, increased lacrimation, dyspnea
- Raised plasma creatinine, proteinuria, hematuria
- Blood disorders including hemolytic anemia, leukopenia, and thrombocytopenia

- **Hydrochlorothiazide**

Hydrochlorothiazide is a representative thiazide diuretic. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 25 mg and 50 mg

- **Uses**

- Alone in mild hypertension, and in combination with other drugs in moderate-to-severe hypertension
- Heart failure (Section 12.4)
- Edema (Section 16)

- **Contraindications**

- Severe renal or severe hepatic impairment
- Hyponatremia, hypercalcemia, refractory hypokalemia, symptomatic hyperuricemia
- Addison's disease

- **Precautions**

- Renal impairment: Appendix D
- Hepatic impairment: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Elderly
- Electrolytes may need to be monitored with high doses or in renal impairment
- May aggravate diabetes mellitus and gout
- May exacerbate systemic lupus erythematosus
- Porphyrria
- **Interactions:** Appendix A

- **Dose**

Hypertension, by mouth

- **ADULT:** 12.5 mg daily, increased to 25–50 mg daily if necessary

- **Adverse effects**

- Fluid and electrolyte imbalance leading to dry mouth, thirst, gastrointestinal disturbances (including nausea, and vomiting), weakness, lethargy, drowsiness, seizures, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, and arrhythmias
- Hypokalemia, hypomagnesemia, hyponatremia, hypochloremic alkalosis, hypercalcemia

- Hyperglycemia, hyperuricemia, gout
- Rash, photosensitivity
- Altered plasma lipid concentration
- Rarely impotence (reversible)
- Blood disorders (including neutropenia, thrombocytopenia)
- Pancreatitis, intrahepatic cholestasis
- Acute renal failure
- Hypersensitivity reactions including pneumonitis, pulmonary edema, and severe skin reactions

- **Methyldopa**

- **Dosage form**

- Tablet: 250 mg

- **Uses**

- Hypertension in pregnancy

- **Contraindications**

- Depression
- Active liver disease
- Pheochromocytomaporphyria

- **Precautions**

- History of hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Blood counts and liver-function tests advised
- History of depression
- Positive direct Coomb's test in up to 20% of patients (affects blood cross-matching)
- Interference with laboratory tests
- Pregnancy: Appendix B

- Breast-feeding: Appendix C
- **Interactions:** Appendix A
- **Skilled tasks:** May impair ability to perform skilled tasks (for example, operating machinery or driving)

○ Dose

Hypertension in pregnancy, by mouth

- **ADULT:** Initially 250 mg 2–3 times daily; gradually increased at intervals of 2 or more days, if necessary; maximum 3 g daily

○ Adverse effects

- Sedation, dizziness, light-headedness, postural hypotension, weakness, fatigue, headache, fluid retention and edema, sexual dysfunction
- Impaired concentration and memory, depression, mild psychosis, disturbed sleep and nightmares
- Drug fever, influenza-like syndrome
- Nausea, vomiting, constipation, diarrhea, dry mouth, stomatitis, sialadenitis
- Liver function impairment, hepatitis, jaundice, rarely fatal hepatic necrosis
- Bone marrow depression, hemolytic anemia, leukopenia, thrombocytopenia, eosinophilia
- Parkinsonism
- Rash including toxic epidermal necrolysis
- Nasal congestion
- Black or sore tongue
- Bradycardia, exacerbation of angina
- Myalgia, arthralgia, paresthesia, Bell's palsy
- Pancreatitis
- Hypersensitivity reactions including lupus erythematosus-like syndrome, myocarditis, pericarditis

- Gynecomastia, hyperprolactinemia, amenorrhea
- Urine darkens on standing

- **Metoprolol**

- **Dosage form**

- Injection solution: 1 mg/ml in 5 ml ampoule
- Tablets: 50 mg and 100 mg

- **Uses**

- Hypertension
- Angina (Section 12.1)
- Migraine prophylaxis (Section 7.2)
- Arrhythmias and control of arrhythmias in surgery, at induction or to control arrhythmias, within 12 hours of infarction

- **Contraindications**

- *See under* Propranolol hydrochloride.

- **Precautions**

- *See under* Propranolol hydrochloride.

- **Dose**

Hypertension, by mouth

- Initially 100 mg daily, increased if necessary to 200 mg daily in 1–2 divided doses; maximum 400 mg daily (but high doses rarely necessary)

Note: Excessive bradycardia can be countered with intravenous injection of atropine sulphate 0.6–2.4 mg in divided doses of 600 micrograms.

- **Adverse effects**

- *See under* Propranolol hydrochloride.

- **Nifedipine**

- **Dosage form**

- Immediate-release and slow-release tablets: 10 mg and 20 mg

- **Uses**

- Hypertension
 - Raynaud's phenomenon
 - Uncomplicated premature labor between 24–33 weeks' gestation (Section 22.2)

- **Contraindications**

- Cardiogenic shock
 - Advanced aortic stenosis
 - Within 1 month of myocardial infarction
 - Unstable or acute attacks of angina
 - Porphyria

- **Precautions**

- Stop if ischemic pain occurs shortly after starting treatment
 - Poor cardiac reserve
 - Heart failure or significantly impaired left ventricular function
 - Severe hypotension
 - Hepatic impairment (reduce dose): Appendix E
 - Diabetes mellitus
 - Breast-feeding: Appendix C
 - Avoid grapefruit juice (may affect nifedipine metabolism)
 - **Interactions:** Appendix A

- **Dose**

Hypertension

- 20–30 mg once daily, increased if necessary to maximum 90 mg once daily

Raynaud's phenomenon

- Initially 5 mg 3 times daily, adjusted according to response to 20 mg 3 times daily

Note: Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of nifedipine, prescribers should specify the brand to be dispensed. Modified-release formulations may not be suitable for dose titration in hepatic disease. Prescription of immediate-release formulations should be avoided in hypertension, especially in those with angina, because it may lead to variation in hypertension and reflective tachycardia that may lead to ischemia in brain vessels and in myocard.

○ **Adverse effects**

- Headache, flushing, dizziness, lethargy
- Tachycardia, palpitations
- Exaggerated fall in blood pressure and reflex tachycardia (may lead to myocardial or cerebrovascular ischemia)
- Gravitational edema
- Rash (erythema multiforme reported), pruritus, urticarial
- Nausea, constipation, or diarrhea
- Increased frequency of micturition
- Eye pain, visual disturbances
- Gum hyperplasia
- Asthenia, paresthesia, myalgia, tremor, gynecomastia
- Depression, telangiectasis, cholestasis, and jaundice reported

- **Verapamil**

- **Dosage form**

- Tablets: 40 mg, 80 mg, and 240 mg (as hydrochloride)
 - Injection: 2.5 mg/ml in 2 ml ampoule

- **Uses**

- Hypertension
 - Angina, including stable, unstable, and Prinzmetal's (Section 12.1)
 - Arrhythmias (Section 12.2)

- **Contraindications**

- See Section 12.1.

- **Precautions**

- See Section 12.1.

- **Dose**

- Hypertension*

- 240–480 mg daily in 2–3 divided doses

- **Adverse effects**

- See Section 12.1.

12.4 Medicines used in heart failure

Treatment of heart failure aims to relieve symptoms, improve exercise tolerance, reduce incidence of acute exacerbations, and reduce mortality. Drugs used to treat heart failure due to left ventricular systolic dysfunction include ACE inhibitors, diuretics, cardiac glycosides, and vasodilators. In addition, measures such as weight reduction, moderate salt restriction, and appropriate exercise should be introduced.

The primary treatment of heart failure is with angiotensin-converting enzyme inhibitors (ACE inhibitors) such as **enalapril**, which can be used in all stages of chronic heart failure to prevent further deterioration and progression of heart disease.

A thiazide diuretic such as **hydrochlorothiazide** (Section 16) is used in the management of mild-to-moderate heart failure when the patient has mild fluid retention and severe pulmonary edema is not present; however, thiazides are ineffective if renal function is poor. In these patients, and in more severe fluid retention, a loop diuretic such as **furosemide** (Section 16) is required. In severe fluid retention, intravenous furosemide produces relief of breathlessness and reduces preload sooner than would be expected from the time of onset of diuresis. Hypokalemia may develop, but this is less likely with the shorter-acting loop diuretics than with the thiazides; however, care is needed to avoid hypotension.

A combination of a thiazide and a loop diuretic may be required to treat refractory edema. The combination often produces a synergistic effect on solute and water excretion, which relieves symptoms in the diuretic-resistant heart failure patient. However, the combination may produce excessive intravascular volume depletion and electrolyte disturbances, including potentially life-threatening hypokalemia.

The aldosterone antagonist spironolactone (Section 16) may be considered for patients with severe heart failure who are already receiving an ACE inhibitor and a diuretic; a low dose of spironolactone (usually 25 mg daily) reduces symptoms and the mortality rate in these patients. Close monitoring of serum creatinine and potassium is necessary with any change in treatment or in the patient's clinical condition.

The beta-blockers bisoprolol and carvedilol can be used in stable heart failure and left ventricular systolic dysfunction. Treatment with beta-blockers should only be undertaken by those experienced in the management of heart failure.

Digoxin, a cardiac glycoside, increases the strength of cardiac muscle contractions and increases cardiac output. In mild heart failure, digoxin inhibits the sympathetic nervous system and produces arterial vasodilation. It produces symptomatic improvement, increases exercise tolerance, and reduces the need for hospitalization, but it does not reduce mortality. It is considered for patients with atrial fibrillation and for selected patients who remain symptomatic despite treatment with an ACE inhibitor, a diuretic, and a suitable beta-blocker.

Vasodilators are used in heart failure to reduce systemic vascular resistance. **Isosorbide dinitrate** (Section 12.1) produces mainly venous dilation, which reduces left ventricular preload, leading to a reduction in pulmonary congestion and dyspnea. **Hydralazine** (Section 12.3) produces mainly arterial vasodilation, which reduces left ventricular afterload, and increases stroke volume and cardiac output. Isosorbide dinitrate and hydralazine can be used in combination when an ACE inhibitor cannot be used, but this combination may be poorly tolerated.

Dopamine, an inotropic sympathomimetic, may be given for short periods in the treatment of severe heart failure. Dosage is critical; at low doses it stimulates myocardial contractility and increases cardiac output; however, higher doses (more than 5 micrograms/kg/min) cause vasoconstriction, with a worsening of heart failure.

- **Digoxin**
 - **Dosage form**
 - Tablets: 0.125 mg and 0.25 mg
 - Injection: 0.1 mg and 0.25 mg/ml in 1 ml ampoule
 - Oral drops: 0.05 mg/ml
 - **Uses**
 - Heart failure
 - Supraventricular arrhythmias (Section 12.2)

- **Contraindications**

- See Section 12.2.

- **Precautions**

- See Section 12.2.

- **Dose**

Heart failure, by mouth

- **ADULT:** 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 125–250 micrograms daily (lower dose more appropriate in the elderly)

Heart failure, emergency loading dose, by intravenous infusion over at least 2 hours

- **ADULT:** 0.75–1 mg

Note: See Section 12.2.

- **Adverse effects**

- See Section 12.2.

- **Dopamine**

Dopamine is a complementary list medicine for inotropic support.

- **Dosage form**

- Injection: 40 mg (hydrochloride)/ml in 5 ml vial

- **Use**
 - Cardiogenic shock including in myocardial infarction and cardiac surgery
- **Contraindications**
 - Tachyarrhythmia, ventricular fibrillation
 - Ischemic heart disease
 - Pheochromocytoma
 - Hyperthyroidism
- **Precautions**
 - Correct hypovolemia before, and maintain blood volume during treatment
 - Correct hypoxia, hypercapnia, and metabolic acidosis before or at same time as starting treatment
 - Use low dose in cardiogenic shock due to myocardial infarction
 - History of peripheral vascular disease (increased risk of ischemia of extremities)
 - Breast-feeding: Appendix C
 - Elderly
 - **Interactions:** Appendix A
- **Dose**

Cardiogenic shock, by intravenous infusion into a large vein

- **ADULT:** 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)

Dilution and administration: According to manufacturer's directions

- **Adverse effects**

- Nausea and vomiting
- Peripheral vasoconstriction
- Hypotension with dizziness, fainting, flushing
- Tachycardia, ectopic beats, palpitations, anginal pain
- Headache, dyspnea
- Hypertension, particularly in overdosage

- **Enalapril**

Enalapril is a representative ACE inhibitor. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 5 mg, 10 mg, and 20 mg

- **Uses**

- Heart failure (with a diuretic)
- Prevention of symptomatic heart failure in patients with left ventricular dysfunction
- Hypertension (Section 12.3)

- **Contraindications**

- See Section 12.3.

- **Precautions**

- See Section 12.3.
- **Interactions:** Appendix A

- **Dose**

Heart failure, asymptomatic left ventricular dysfunction, by mouth

- **ADULT:** 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

- **Adverse effects**

- See Section 12.3.

- **Furosemide**

- **Dosage form**

- Tablets: 20 mg and 40 mg
- Injection: 10 mg/ml in 2 ml ampoule
- See Section 16.

- **Hydrochlorothiazide**

Hydrochlorothiazide is a representative thiazide diuretic. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 25 mg and 50 mg

- **Uses**

- Heart failure
- Hypertension (Section 12.3)
- Edema (Section 16)

- **Contraindications**

- See Section 12.3.

- **Precautions**

- See Section 12.3.

- **Dose**

Heart failure, by mouth

- **ADULT:** Initially 25 mg daily on rising (reduce to 12.5 mg daily in the **ELDERLY**), increased to 50 mg daily, if necessary

- **Adverse effects**

- See Section 12.3.

12.5 ANTITHROMBOTIC MEDICINES

Anticoagulants such as heparin sodium and warfarin prevent thrombus formation or the extension of an existing thrombus. Antiplatelet drugs such as **acetylsalicylic acid** (aspirin) also help to inhibit thrombus formation by decreasing platelet aggregation.

Thrombolytics (fibrinolytics) such as **streptokinase** are used to break up thrombi; they are used to treat acute myocardial infarction, extensive deep vein thrombosis, major pulmonary embolism, and acute arterial occlusion.

Myocardial infarction

Management of myocardial infarction consists of two phases:

- Initial management of the acute attack
- Long-term management, including prevention of further attacks

Initial management

Oxygen (Section 1.1) should be given to all patients, except those with severe chronic obstructive pulmonary disease.

Pain and anxiety are relieved by slow intravenous injection of an opioid analgesic such as morphine (Section 2.2). Metoclopramide (Section 17.2) may also be given by intramuscular injection to prevent and treat nausea and vomiting caused by morphine.

Acetylsalicylic acid (aspirin) 150–300 mg by mouth (preferably chewed or dispersed in water) is given immediately for its antiplatelet effect.

Thrombolytic drugs such as streptokinase help to restore perfusion and thus relieve myocardial ischemia; they should ideally be given within 1 hour of infarction (use after 12 hours requires specialist advice). Antibodies to streptokinase appear 4 days after use and streptokinase should not be given to the patient again after this time.

Nitrates (Section 12.1) may also be given to relieve ischemic pain.

Early administration of a beta-blocker such as atenolol (Section 12.1) has been shown to reduce both early mortality and the recurrence rate of myocardial infarction; initial intravenous administration is followed by long-term oral treatment (unless the patient has contraindications).

ACE inhibitors such as enalapril (Section 12.4) have also been shown to be beneficial in initial management (unless patient has contraindications), when given within 24 hours, and if possible continued for at least 5–6 weeks.

If arrhythmias occur, they should be treated aggressively (*see* Section 12.2), but the likelihood of arrhythmia decreases rapidly over the first 24 hours after infarction. Ventricular fibrillation should be treated immediately with a defibrillator; if this alone is ineffective, the anti-arrhythmic drug lidocaine (Section 12.2) should be given.

All patients should be closely monitored for hyperglycemia; those with diabetes mellitus or raised blood glucose concentration should receive insulin (*see* Section 18.5).

Long-term management

Acetylsalicylic acid (aspirin) should be given to all patients unless it is contraindicated. The prolonged antiplatelet effect has been shown to reduce the rate of reinfarction.

Treatment with beta-blockers should be continued for at least 2–3 years. Verapamil is sometimes useful if a beta-blocker cannot be used (*see* Section 12.1).

ACE inhibitors such as enalapril (Section 12.4) should also be used since they reduce mortality, particularly in patients with left ventricular dysfunction.

Nitrates (Section 12.1) may be required for patients with angina.

The use of statins (Section 12.6) may also be considered in patients with high risk of recurrence.

Stroke

Stroke (cerebrovascular accident) may be ischemic or hemorrhagic; precise diagnosis is essential, as management for the two types of stroke is quite different.

Primary prevention of both types of stroke includes management of high blood pressure, stopping smoking, weight reduction, and cholesterol reduction. Atrial fibrillation, acute myocardial infarction, and valvular disease may produce embolism and ischemic stroke. Prophylaxis in patients at risk of ischemic stroke includes antiplatelet drugs such as acetylsalicylic acid or oral anticoagulants such as warfarin. Treatment of acute ischemic stroke includes use of acetylsalicylic acid (aspirin) given within 48 hours of onset and, in selected patients, anticoagulants such as heparin sodium (Section 10.2) and streptokinase (streptokinase should be used with caution due to risk of exacerbation of bleeding). Long-term therapy with acetylsalicylic acid reduces the risk of having another stroke.

Antiplatelet drugs are **not** used in the management of hemorrhagic stroke because they

can exacerbate bleeding. Treatments include careful lowering of very high blood pressure (see Section 12.3) and surgery where appropriate.

Acetylsalicylic acid is normally given for at least 1 year after coronary artery bypass surgery. It is also given to patients with prosthetic heart valves who have had cerebral embolism despite warfarin treatment.

- **Acetylsalicylic acid (aspirin)**

- **Dosage form**

- Tablets: 75 mg, 100 mg, 325 mg, and 500 mg

- **Uses**

- Acute myocardial infarction, acute ischemic stroke, prophylaxis of cerebrovascular disease or myocardial infarction
 - Pyrexia, pain, inflammation (Section 2.1)
 - Migraine (Section 7.1)

- **Contraindications**

- See Section 2.1.

- **Precautions**

- See Section 2.1.
 - **Interactions:** Appendix A

- **Dose**

- Prophylaxis of cerebrovascular disease or myocardial infarction, by mouth*

- **ADULT:** 75–100 mg daily

Treatment of acute myocardial infarction, acute ischemic stroke, by mouth

- **ADULT:** 150–300 mg

- **Adverse effects**

- Bronchospasm
- Gastrointestinal hemorrhage (rarely major), also other hemorrhage (for example, subconjunctival)
- *See also* Section 2.1.

- **Streptokinase**

Streptokinase is a complementary drug; it is used in the management of myocardial infarction and thromboembolism.

- **Dosage form**

- Powder for injection: 0.25, 0.75, and 1.5 million IU in vial

- **Uses**

- Life-threatening deep-vein thrombosis, pulmonary embolism, acute arterial thromboembolism
- Acute myocardial infarction

- **Contraindications**

- Repeat use of streptokinase beyond 4 days of first administration
- Recent hemorrhage, surgery (including dental), parturition, trauma
- Heavy vaginal bleeding
- Hemorrhagic stroke, history of cerebrovascular disease (especially recent or if residual disability)
- Coma
- Severe hypertension
- Coagulation defects

- Bleeding diatheses, aortic dissection
 - Risk of gastrointestinal bleeding (such as recent history of peptic ulcer, esophageal varices, or ulcerative colitis)
 - Acute pancreatitis
 - Severe liver disease
 - Acute pulmonary disease with cavitation
 - Previous allergic reactions
- **Precautions**
- Risk of bleeding from any invasive procedure (including injection)
 - External chest compression
 - Pregnancy: Appendix B
 - Abdominal aneurysm or where thrombolysis may give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolization)
 - Diabetic retinopathy (small risk of retinal hemorrhage)
 - Recent or concurrent anticoagulant treatment

○ **Dose**

Acute myocardial infarction (preferably within 1 hour of infarction), by intravenous infusion

- **ADULT:** 1,500,000 IU over 60 minutes

Thrombosis, by intravenous infusion

- **ADULT:** 250,000 IU over 30 minutes, followed by 100,000 IU every hour for 12–72 hours, according to condition with monitoring of clotting parameters

○ **Adverse effects**

- Nausea and vomiting

- Bleeding, usually limited to site of injection but internal bleeding including intracranial hemorrhage may occur (if serious bleeding occurs, discontinue infusion; coagulation factors may be required)
- Hypotension, arrhythmias (particularly in myocardial infarction)
- Allergic reactions including rash, flushing, uveitis, and anaphylaxis
- Fever, chills, back or abdominal pain
- Guillain-Barré syndrome reported rarely

12.6 LIPID-LOWERING AGENTS

The primary aim of therapy is to reduce progression of atherosclerosis and to improve survival in patients with established cardiovascular disease, to reduce premature cardiac morbidity and mortality in people at high risk of cardiovascular events, and to prevent pancreatitis due to hypertriglyceridemia. Before initiation of treatment some measures, such as control of food regimen, lowering blood pressure, and cessation of smoking, should be considered.

Beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG Co A) reductase inhibitors, often referred to as “statins,” are potent and effective lipid-lowering drugs with a good tolerability profile. Statins have been shown to reduce the incidence of fatal and non-fatal myocardial infarction, stroke, and mortality (all causes), as well as the need for coronary bypass surgery. They are recommended for primary and secondary prevention of atherosclerotic cardiovascular disease in high-risk patients.

- **Atorvastatin**

- **Dosage form**

- Tablets: 5 mg, 10 mg, 20 mg, and 40 mg* (as calcium trihydrate)

- **Uses**

- Primary hypercholesterolemia, heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or

combined (mixed) hyperlipidemia in patients who have not responded adequately to diet and other appropriate measures

- Prevention of cardiovascular events in patients at high risk of a first cardiovascular event

- **Precautions**

- Hypothyroidism should be managed adequately before starting treatment with a statin. Patients with hypothyroidism should receive adequate thyroid replacement therapy before assessing the requirement for lipid-regulating treatment because correcting hypothyroidism itself may resolve the lipid abnormality. Untreated hypothyroidism increases the risk of myositis with lipid-regulating drugs.
- Statins should be used with caution in those with a history of liver disease or with a high alcohol intake—*see also* Hepatic impairment below. There is little information available on a rational approach to liver-function monitoring; however, a NICE¹ guideline suggests that liver enzymes should be measured before treatment, and repeated within 3 months and at 12 months of starting treatment, unless indicated at other times by signs or symptoms suggestive of hepatotoxicity.
- Patients with serum transaminases that are raised but less than 3 times the upper limit of the reference range should not be routinely excluded from statin therapy. Those with serum transaminases of more than 3 times the upper limit of the reference range should discontinue statin therapy.
- Statins should be used with caution in those with risk factors for myopathy or rhabdomyolysis; patients should be advised to report unexplained muscle pain.
- Statins should be avoided in acute porphyria (prevalence of about 1 in 10,000 of the population). Great care must be taken when prescribing for patients with acute porphyria, since certain drugs can induce acute

¹ National Institute for Health and Care Excellence (NICE). NICE clinical guideline 67. 2008. Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. London: NICE.

porphyric crises. Since acute porphyrias are hereditary, relatives of affected individuals should be screened and advised about the potential danger of certain drugs. Treatment of serious or life-threatening conditions should not be withheld from patients with acute porphyria. When there is no safe alternative, treatment should be started and urinary porphobilinogen excretion should be measured regularly; if it increases or symptoms occur, the drug can be withdrawn and the acute attack treated.

- If an acute attack of porphyria occurs during pregnancy, contact an expert porphyria service for further advice. Monitor cognitive and neurological function, monitor fetal growth; also hemorrhagic stroke.
- Hepatic impairment: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Dose**

Primary hypercholesterolemia and combined hyperlipidemia

- **ADULT:** Usually 10 mg once daily; if necessary, may be increased at intervals of at least 4 weeks to maximum 80 mg once daily
- **CHILD** under 18 years: Initially 10 mg once daily, increased if necessary at intervals of at least 4 weeks to usual maximum 20 mg once daily

Familial hypercholesterolemia

- **ADULT:** Initially 10 mg daily, increased at intervals of at least 4 weeks to 40 mg once daily; if necessary, further increased to maximum 80 mg once daily (or 40 mg once daily combined with anion-exchange resin in heterozygous familial hypercholesterolemia)
- **CHILD** under 18 years: Initially 10 mg once daily, increased if necessary at intervals of at least 4 weeks to usual maximum 20 mg once daily (max. 80 mg once daily in homozygous familial hypercholesterolemia)

Prevention of cardiovascular events

- **ADULT:** Initially 10 mg once daily, adjusted according to response

Note: Maximum 10 mg daily with concomitant ciclosporin or tipranavir combined with ritonavir

○ **Adverse effects**

- The statins can cause various muscular side effects, including myositis, which can lead to rhabdomyolysis. Muscular effects are rare but often significant.
- Statins can cause gastrointestinal disturbances, and very rarely pancreatitis.
- They can also cause altered liver function tests, and rarely hepatitis and jaundice; hepatic failure has been reported very rarely.
- Other side effects include sleep disturbance, headache, dizziness, depression, paresthesia, asthenia, peripheral neuropathy, amnesia, fatigue, sexual dysfunction, thrombocytopenia, arthralgia, visual disturbance, alopecia, and hypersensitivity reactions (including rash, pruritus, urticaria, and very rarely lupus erythematosus-like reactions).
- In very rare cases, statins can cause interstitial lung disease; if patients develop symptoms such as dyspnea, cough, or weight loss, they should seek medical attention.

• **Cholestyramine**

○ **Dosage form**

- Oral ingestion powder: 4 g per sachet (anhydrous)

○ **Uses**

- Hyperlipidemias, particularly type IIa, in patients who have not responded adequately to diet and other appropriate measures

- Primary prevention of coronary heart disease in men aged 35–59 years with primary hypercholesterolemia who have not responded to diet and other appropriate measures
 - Pruritus associated with partial biliary obstruction and primary biliary cirrhosis
 - Diarrheal disorders; cholestamine relieves diarrhea and pruritus by forming an insoluble complex with bile acids in the intestines.
- **Contraindication**
 - Complete biliary obstruction
 - **Precautions**
 - Bile acid sequestrants interfere with the absorption of fat-soluble vitamins; supplements of vitamins A, D, K, and folic acid may be required when treatment is prolonged.
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Dose**

Lipid reduction

- **ADULT:** Initially 4 g daily increased by 4 g at weekly intervals to 12–24 g daily in 1–4 divided doses, then adjusted as required; maximum 36 g daily

Pruritus

- **ADULT:** 4–8 g daily in a suitable liquid

Diarrheal disorders

- **ADULT:** Initially 4 g daily increased by 4 g at weekly intervals to 12–24 g daily in a suitable liquid in 1–4 intervals doses, then adjusted as required; maximum 36 g daily

Pruritus associated with partial biliary obstruction and primary biliary cirrhosis, diarrhea associated with Crohn's disease, ileal resection, vagotomy, diabetic vagal neuropathy, and radiation, by mouth

- **CHILD** 1 month–1 year: 1 g once daily in a suitable liquid by mouth, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 9 g daily).
- **CHILD** 1–6 years: 2 g once daily in a suitable liquid by mouth, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 18 g daily).
- **CHILD** 6–12 years: 4 g once daily in a suitable liquid by mouth, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 24 g daily).
- **CHILD** 12–18 years: 4–8 g once daily in a suitable liquid by mouth, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 36 g daily).

Patient advice: Other drugs should be taken at least 1 hour before or 4–6 hours after colestyramine to reduce possible interference with absorption.

Note: For treatment of diarrhea induced by bile acid malabsorption, if no clinical response within 3 days, start alternative treatment.

○ **Adverse effects**

- As bile acid sequestrants are not absorbed, gastrointestinal side effects predominate. Constipation is common, but diarrhea has occurred, as have nausea, vomiting, and gastrointestinal discomfort.
- Hypertriglyceridemia may be aggravated.

- An increased bleeding tendency has been reported due to hypoprothrombinemia associated with vitamin K deficiency.
- Intestinal obstruction reported rarely and hyperchloremic acidosis reported on prolonged use.

Note: The contents of each sachet should be mixed with at least 150 ml of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, and pulpy fruits with a high moisture content.

- **Fenofibrate**

- **Dosage form**

- Capsule: 200 mg

- **Uses**

- Adjunct to diet and other appropriate measures in mixed hyperlipidemia if statin contraindicated or not tolerated, or in severe hypertriglyceridemia
- Adjunct to statin in mixed hyperlipidemia if triglycerides and HDL-cholesterol inadequately controlled in patient at high cardiovascular risk; although a fibrate can reduce the risk of coronary heart disease events in those with low HDL-cholesterol or with raised triglycerides, a statin should be used first. Fibrates are first-line therapy only in those whose serum-triglyceride concentration is greater than 10 mmol/l or in those who cannot tolerate a statin.

- **Contraindications**

- Gall bladder disease
- Pancreatitis (unless due to severe hypertriglyceridemia)
- Photosensitivity to ketoprofen

- **Precautions**

- Correct hypothyroidism before initiating treatment; patients with hypothyroidism should receive adequate thyroid replacement therapy before assessing the requirement for lipid-regulating treatment because correcting hypothyroidism itself may resolve the lipid abnormality. Untreated hypothyroidism increases the risk of myositis with lipid-regulating drugs.
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Breast-feeding: Appendix C
 - Pregnancy: Appendix B
 - **Interactions:** Appendix A
- **Dose**
- **ADULT:** 1 capsule daily (dose form not appropriate for children or in renal impairment)
- **Adverse effects**
- Gastrointestinal disturbances, anorexia
 - Less commonly cholestasis, weight gain, dizziness, headache, fatigue, drowsiness, renal impairment, raised serum creatinine (unrelated to renal impairment), erectile dysfunction, myotoxicity (with myasthenia or myalgia)—special risk in renal impairment (*see* Precautions), urticaria, pruritus, photosensitivity reactions
 - Very rarely gallstones, hypoglycemia, anemia, leukopenia, thrombocytopenia, increased platelet count, alopecia, Stevens-Johnson syndrome, and toxic epidermal necrolysis
 - Also less commonly pancreatitis, pulmonary embolism
 - Rarely hepatitis and also reported interstitial pneumopathies

SECTION 13: Dermatological medicines (topical)

LML strengths and dosage forms are marked in *italic* with an asterisk.

13.1 ANTIFUNGAL MEDICINES

Ringworm

Benzoic acid and methylrosanilinium chloride (gentian violet) solution are inexpensive and effective fungistatic compounds for the treatment of dermatophyte infections such as ringworm. Minor skin lesions due to ringworm can be cleared with repeated applications of compound benzoic acid ointment (Whitfield's ointment), which combines the fungistatic action of **benzoic acid** with the keratolytic action of **salicylic acid**. However, the most effective topical treatment for dermatophyte infections is a cream containing an imidazole such as **miconazole** or clotrimazole, which is effective for long-established lesions but is more expensive than compound benzoic acid ointment. Extensive and generalized infections of the skin, nails, and scalp should be treated systemically for several weeks with griseofulvin or fluconazole.

Scalp ringworm (*Tinea capitis*) typically appears as a patch of scaling alopecia, or a swollen inflammatory area (*Tinea kerion*). Mild forms may remit spontaneously at puberty. Inflamed lesions should be treated systemically with griseofulvin (Section 6.3). Application of miconazole cream may accelerate healing of scaly lesions.

Ringworm on the body (*Tinea corporis*) can also be cleared with **compound benzoic acid** ointment or a topical imidazole such as **miconazole**. In resistant cases, a 4-week course of oral griseofulvin is required.

Foot ringworm (*Tinea pedis* or athlete's foot) is usually treated topically. Compound benzoic acid ointment should be applied twice daily to all infected areas and all toe clefts

for at least 4 weeks. Systemic therapy with griseofulvin or fluconazole may be required if the foot is extensively infected.

Tinea pedis commonly recurs and may be treated with miconazole cream. Severe weeping lesions respond to frequent soaking in solutions of 1:10,000 potassium permanganate; systemic antifungals may also be needed.

Nail infections (onychomycosis, *tinea unguium*) are difficult to treat; fingernails may require 6 months of treatment with oral griseofulvin and toenails up to 12 months or more of the same treatment. Approximately 60% of nail infections either do not respond or relapse after treatment with griseofulvin.

Ringworm of the groin (*Tinea cruris*) is usually limited to the skin of the inner thigh in contact with the scrotum. Flexural eczema, often superinfected with *Candida* or bacteria, occurs in the same site. The latter is frequently treated with combined antifungal/corticosteroid preparations, but must not be treated with a corticosteroid alone, as this will worsen the condition. An imidazole cream such as miconazole applied daily for 2 weeks is usually effective. Lesions unresponsive to topical preparations can usually be cleared with a 4-week course of griseofulvin (Section 6.3).

Candidiasis

Candida can infect the oral cavity, the vagina, or the skin. Cutaneous lesions tend to occur in patients with diabetes mellitus and some chronic debilitating conditions, including hypoparathyroidism, and various congenital disorders of the immune system. The most severe infections with *Candida* are now seen in patients with HIV infection.

Cutaneous candidiasis usually responds to twice-daily applications of creams containing either **miconazole** or **clotrimazole**. Chronic *Candida paronychia*, which can result ultimately in nail dystrophy, is more difficult to treat. Treatment should be based on determination of the underlying cause and its reduction or elimination; hands and folds of the nail must be kept dry and daily application of an imidazole cream for several months

may be required, ensuring penetration of the cleft between the nail plate and the swollen skin around the nail.

Pityriasis versicolor

Pityriasis (Tinea) versicolor is caused by a commensal yeast. Application of **sodium thiosulfate** solution, 15% twice daily for 4 weeks, is usually effective, although areas of depigmentation on darker skin remain after completion of treatment. However, relapses can be frequent, probably because much of the infected area may appear normal and thus be left untreated. Better results have been reported with topical applications of **miconazole** or **selenium sulfide**.

- **Benzoic acid + salicylic acid**

Also known as Whitfield's ointment

- **Dosage form**

- Cream or ointment: 6% + 3%

- **Uses**

- Mild dermatophyte infections, particularly *Tinea pedis* and *Tinea corporis*

- **Administration**

Fungal skin infections

- **ADULT** and **CHILD**: Apply directly to the affected area twice daily until the infected skin is shed (usually at least 4 weeks).

- **Adverse effects**

- Occasionally localized, mild inflammatory reaction

- **Ketoconazole**

- **Dosage form**

- Cream: 2%

- **Uses**

- Fungal skin infections
 - Systemic or resistant fungal infections
 - Vulval candidiasis

- **Precautions**

- Avoid contact with eyes and mucous membranes.

- **Dose**

- Tinea pedis*

- Apply twice daily.

- Other fungal infections*

- Apply 1–2 times daily.

- **Adverse effects**

- Occasional local irritation and hypersensitivity reactions include mild burning sensation, erythema, and itching. Treatment should be discontinued if these are severe.

- **Ketoconazole**

- **Dosage form**

- Shampoo: 2%

- **Uses**

- Treatment of seborrheic dermatitis and dandruff, treatment of *Pityriasis versicolor*

- **Dose**

Treatment of seborrheic dermatitis and dandruff

- Apply twice weekly for 2–4 weeks (prophylaxis: apply once every 1–2 weeks).

Treatment of pityriasis versicolor

- Apply once daily for maximum 5 days. Leave preparation on for 3–5 minutes before rinsing.

- **Tolnaftate**

- **Dosage form**

- Skin ointment: 1%

- **Uses**

- Treatment and prevention of superficial dermatophyte infections and *Pityriasis versicolor*

- **Precautions**

- Avoid contact with eyes.

- **Dose**

- **ADULT** and **CHILD**: Small amount of topical ointment is applied to affected area 2 times a day for 2–3 weeks (for 6 weeks, in case of thickening of skin). Treatment should be continued until complete recovery.

- **Adverse effects**

- Sensitization of skin, mild irritation, skin itching, contact dermatitis, stinging

13.2 ANTI-INFECTIVE MEDICINES

Staphylococcal infections of the skin (such as impetigo, folliculitis, and furunculi) and streptococcal infections (such as cellulitis and erysipelas) are very common where the climate is hot and humid, where standards of hygiene are compromised, and in immunodeficient patients.

In all skin infections, an important part of treatment is cleansing and thorough drying. Washing with soap and water will often help to prevent infection. Light localized infections can often be treated effectively with an antiseptic solution such as chlorhexidine. Superficial crusts should be gently washed with soap and water or a weak solution of aluminium diacetate or a 0.01% solution of **potassium permanganate**. Infected burns should be treated with **silver sulfadiazine**, which is bactericidal against both gram-positive and gram-negative organisms.

Topical formulations containing mupirocin 2% can be used to treat bacterial infections of the skin such as impetigo and folliculitis. To prevent the development of resistance, mupirocin should not be used for more than 10 days. Topical preparations containing **neomycin sulfate** and **bacitracin** are also widely used, but these carry a risk of sensitization, particularly with continued or repeated use.

Topical use of preparations containing antimicrobials that are widely used to treat skin infections systemically should be avoided. These include the penicillins, the sulfonamides, streptomycin, and gentamicin, which should be reserved for the systemic treatment of infections because of the possibility of inducing sensitivity and favoring the emergence of resistant organisms. Only widespread superficial or deep-seated skin infections associated with fever require treatment with a systemic antibiotic.

Whenever possible, the choice of an antimicrobial should be based on the results of sensitivity tests.

- **Methylrosanilinium chloride (gentian violet)**

- **Dosage form**

- Topical solution: 0.5% and 1%
 - Powder: In 25 g bottle (for preparation of different dilutions)

- **Uses**

- Superficial fungal and bacterial infections

- **Contraindications**

- Excoriated or ulcerated lesions, broken skin, mucous membranes
 - Porphyria

- **Administration**

- Skin infections*

- **ADULT** and **CHILD:** Apply directly to affected area 2 or 3 times daily for 3 days.

- **Adverse effects**

- Severe irritation (discontinue treatment)
 - Temporary staining of skin, permanent staining of fabrics
 - Animal carcinogenicity (restricted use in some countries)

- **Mupirocin**

- **Dosage form**

- Ointment: 2% in 10 g tube

- **Uses**

- Bacterial skin infections
- Mupirocin is not related to any other antibacterial in use; it is effective for skin infections, particularly those due to gram-positive organisms but it is not indicated for pseudomonal infection. Although *Staphylococcus aureus* strains with low-level resistance to mupirocin are emerging, it is generally useful in infections resistant to other antibacterials. To avoid the development of resistance, mupirocin should not be used for longer than 10 days and local microbiology advice should be sought before using it in hospital. In the presence of mupirocin-resistant MRSA infection, a topical antiseptic such as povidone-iodine, chlorhexidine, or alcohol can be used; their use should be discussed with the local microbiologist.

- **Precautions**

- Renal impairment: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C

- **Administration**

- **ADULT** and **CHILD** over 1 year: Apply up to 3 times daily for up to 10 days.
- **CHILD** 1 month–18 years: Apply up to 3 times daily for up to 10 days.

- **Adverse effects**

- Local reactions including urticaria, pruritus, burning sensation, rash

- **Neomycin sulfate + bacitracin**

Bacitracin is a representative topical antibacterial. Various medicines can serve as alternatives.

- **Dosage form**

- Topical ointment: Neomycin sulfate 5 mg with bacitracin 500 IU/g, in 15 g tube

- **Uses**

- Superficial bacterial infections of the skin due to *Staphylococcus* and *Streptococcus*.

- **Contraindication**

- **Neonates**

- **Precautions**

- Avoid application to substantial areas of skin or to broken skin (risk of significant systemic absorption).
- Overgrowth of resistant organisms on prolonged use

- **Administration**

Bacterial skin infections (short-term use)

- **ADULT** and **CHILD** over 2 years: Apply sparingly to the affected areas 3 times daily.

- **Adverse effects**

- Hypersensitivity, especially to neomycin, causing reddening and scaling
- Anaphylaxis reported rarely
- Systemic absorption leading to irreversible ototoxicity, particularly in children, the elderly, and in those with renal impairment

- **Neomycin**

- **Dosage form**

- Ointment: 0.5% in 15 mg tube for external use

- **Uses**
 - Bacterial skin infections
- **Contraindication**
 - Neonates
- **Precautions**
 - If large areas of skin are being treated, ototoxicity may be a hazard, particularly in children, in the elderly, and in those with renal impairment.
 - Avoid continuous administration.
 - Monitor renal and atrial auditory activities. Some amount of neomycin may be absorbed in hepatic failure patients and cause auditory toxicity.
 - Neomycin may cause sensitization and there is cross-sensitivity with other aminoglycoside antibiotics, such as gentamicin.
- **Dose**
 - See manufacturer's leaflet.
- **Adverse effects**
 - Sensitization
- **Potassium permanganate**
 - **Dosage form**
 - Aqueous solution: 0.01%
 - Powder: 0.01%
 - Note:*** Potassium permanganate is sometimes supplied as an aqueous stock solution of 1 in 1,000 (0.1%) for dilution before use.
 - **Uses**

- Wet dressings to assist healing of suppurating superficial wounds, tropical ulcers, pemphigus, impetigo
- *Tinea pedis* (Section 13.1)
- **Contraindication**
 - Avoid occlusive dressings.
- **Precautions**
 - Irritant to mucous membranes
- **Administration**

Impetigo

- **ADULT** and **CHILD:** Apply dressings soaked in 0.01% (1:10,000) solution until superficial crusts can be gently separated.

Suppurating superficial wounds and tropical ulcers

- **ADULT** and **CHILD:** Apply dressings soaked in 0.01% (1:10,000) solution to the affected area, changing dressings 2 or 3 times daily; tropical ulcers also require treatment with procaine benzylpenicillin for 2–4 weeks (Section 6.2.1).

Tinea pedis

- **ADULT** and **CHILD:** Bathe severe weeping lesions in a 1:10,000 solution every 8 hours.

- **Adverse effects**
 - Local irritation
 - Skin and fabrics stained brown

- **Silver sulfadiazine**

- **Dosage form**

- Cream: 1% in 20 g tube

- **Uses**

- Prophylaxis and treatment of infection in burns

- **Contraindications**

- Hypersensitivity to sulfonamides
- Pregnancy: Appendix B
- **Neonates**

- **Precautions**

- Renal impairment: Appendix D
- Hepatic impairment: Appendix E
- G6PD deficiency
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Administration**

- Infection in burns*

- **ADULT** and **CHILD:** Apply using aseptic technique once daily (more frequently if volume of exudate is large) while there is a possibility of infection, or until healing is complete.

- **Adverse effects**

- Allergic reactions including rash, burning, and itching
- Argyria and sulfonamide-induced systemic toxicity, including blood disorders following application to large areas or prolonged use

- Transient leukopenia reported

- **Tetracycline**

- **Dosage form**

- Ointment: 3% in 15 g tube (as hydrochloride)

- **Uses**

- Bacterial skin infections

- **Precautions**

- Extensive areas of the skin
 - Unresponsive infections
 - Avoid contact with eyes

- **Administration**

- Bacterial skin infections*

- Apply 1–3 times daily.

- **Adverse effects**

- Rarely allergic reactions

- **Sulfur + salicylic acid**

- **Dosage form**

- Topical ointment: Sulfur 2% + salicylic acid 1%

- **Uses**

- Dandruff and other scalp diseases

- **Contraindications**

- Hypersensitivity to sulfur, salicylic acid (aspirin)

- **Precautions**

- This drug should only be used on scalp and skin; avoid using on skin abrasions or cuts.
- Keep this medicine away from the eyes.
- Avoid overdosage.
- Pregnancy: Appendix B
- Breast-feeding: Appendix C

- **Adverse effects**

- Burning, redness, and desquamation of the skin in the application site, flushing, scalp blisters and peeling, skin lesions, swelling and itching (especially on face, tongue, and throat), severe drowsiness and respiratory disorders

- **Zinc oxide**

- **Dosage form**

- Ointment: 10% and 20% in 20 g tube

- **Uses**

- Eczema and protection of skin from lesions caused by urine and lesions caused by using diapers or pumpers (nappy rash)

- **Precautions**

- Avoid contact with eyes.

- **Administration**

- Apply to skin according to need.

13.3 ANTI-INFLAMMATORY AND ANTIPRURITIC MEDICINES

Contact dermatitis

Contact dermatitis can result from an allergic or irritant skin reaction. Removal of the substance provoking the reaction is the first step in treating this condition. Mild cases of contact dermatitis can be treated with topical **hydrocortisone**, which suppresses inflammation. A short course of oral prednisolone (Section 3) or a topical corticosteroid such as **betamethasone** should be considered for more severe cases and for suppression of severe acute reactions associated with blistering, exudation, and edema. Soaking in clean water or mild saline solution is recommended in the acute stages of severe dermatitis.

Pruritus

Pruritus, or itching, is a common symptom of many skin diseases. However, systemic disease, contact with certain substances, conditions that dry the skin, stress, and extremes of temperature may also be a cause. Thus, an important part of treatment for pruritus is to eliminate or minimize any underlying cause for the irritation.

Emollients, such as aqueous creams and emulsifying creams, are of value in pruritus associated with dry skin or in pruritus occurring in an otherwise healthy elderly individual; the value of calamine lotion in such cases is, however, uncertain. Systemic antihistamines, such as oral chlorphenamine (Section 3), may relieve generalized pruritus. Topical corticosteroids, such as **hydrocortisone** or **betamethasone**, are appropriate for treating insect stings.

Atopic dermatitis

Atopic dermatitis (or eczema) is a common skin disorder that mainly occurs in infants and children; it is associated with intense itching and areas of red skin. Pruritus may be partially relieved by applying astringent aluminium diacetate solution to exudative

lesions and emollients to lichenified plaques. Topical **hydrocortisone** should be applied in short courses of 1–2 weeks to treat even mild areas of involvement. The use of topical **betamethasone** should be reserved for the treatment of persistent localized the dermatitis in adults. Topical antihistamines are not effective and should be avoided because of the risk of sensitization. However, a sedative antihistamine such as chlorphenamine can be given at night to calm pruritus and facilitate sleep (Section 3). A secondary infection, often involving *Staphylococcus aureus*, may be responsible for exacerbations; in such cases, a short course (7–10 days) of an oral antibiotic such as erythromycin can be given.

Seborrheic dermatitis

Use of a keratolytic shampoo and exposure to ultraviolet light reduce both the inflammation and the scaling resulting from seborrheic dermatitis of the scalp (dandruff). The shampoo should be massaged into the scalp, immediately rinsed off, and then reapplied until a foam is produced, leaving the second application in contact with the scalp for at least 5 minutes. Selenium sulfide, which has both antifungal and keratolytic properties, is widely used in many proprietary shampoos. Preparations containing a combination of sulfur and salicylic acid, which have an additional antimicrobial action, are also effective.

Ichthyosis

In ichthyosis, emollients should be applied daily (or more frequently in severe cases) to affected skin. The addition of a keratolytic, such as salicylic acid (Section 13.5) can be helpful.

Lichen planus

Lichen planus is a chronic, papular, pruritic skin eruption that occurs typically in middle age and later life; the condition is often mild and may need no treatment. In generalized mild cases, a topical corticosteroid, such as hydrocortisone, may relieve pruritus. In severe forms, systemic treatment may be necessary; oral corticosteroids (such as prednisolone), ciclosporin, and retinoids have been used.

Pityriasis rosea

In pityriasis rosea, a common self-limiting dermatosis that is probably of infective origin, **calamine** lotion helps to relieve pruritus in most cases. If it does not, topical application of **hydrocortisone** in a concentration not exceeding 1% may be tried.

- **Calamine lotion**

Calamine is a representative topical antipruritic. Various medicines can serve as alternatives.

- **Dosage form**

- Topical cream ($\text{ZnO} + \text{Fe}_2\text{O}_3$): 8% in 30 g tube
 - Topical lotion: 8% in 60 ml bottle
 - Powder

- **Uses**

- Mild pruritus

- **Dose**

- **ADULT** and **CHILD**: Apply liberally to the entire affected area 3–4 times daily.

- **Hydrocortisone**

Hydrocortisone is a representative mild topical corticosteroid. Various medicines can serve as alternatives.

- **Dosage form**

- Ointment: 1% (acetate) in 15 g tube

- **Uses**

- Contact dermatitis, atopic dermatitis (eczema), lichen planus
 - Pityriasis rosea
 - Intractable pruritus and phototoxic reactions, including polymorphic light eruptions and actinic prurigo
 - Short-term treatment of psoriasis of the face and flexures
- **Contraindications**
 - Untreated skin infections, broken skin, rosacea, acne, perioral dermatitis
 - **Precautions**
 - Children (avoid prolonged use)
 - Concomitant use with occlusive dressings (may increase penetration into keratinized lesions)
 - Secondary infection requires treatment with an appropriate antimicrobial
 - **Administration**

Inflammatory skin conditions

- **ADULT** and **CHILD**: Apply sparingly to the affected area, 1–2 times daily until improvement occurs, then less frequently.
- **Adverse effects**
 - Exacerbation of local infection
 - Atrophic changes (*see under* Betamethasone) less likely with mild corticosteroids, but infants and children particularly susceptible
 - Contact dermatitis
 - Perioral dermatitis
 - Hypertrichosis reported

- **Betamethasone + neomycin**

Betamethasone is a representative of the steroids that reduces skin inflammation and irritations. Neomycin is an antibacterial medicine that is effective against bacterial skin infections.

- **Dosage form**

- Skin ointment: Betamethasone valerate 0.1 % and neomycin sulfate 0.5% in 15 g tube

- **Uses**

- Reduction of redness and irritation in some skins disorders including eczema, psoriasis, dermatitis, and insect bites when infected

- **Contraindications**

- Hypersensitivity to any of the above combinations
- Children younger than 2 years
- Acne vulgaris
- Rosacea
- Periocular dermatitis
- Viral infections
- Fungal infections
- Skin blisters or ulcers caused by infection and infection of the external ear

- **Administration**

- Applied to skin 2 or 3 times a day.

- **Adverse effects**

- Burning sensation or irritation in the application area, excessive hair growth and changes in the color of the skin, thinning of the skin

13.4 ASTRINGENT MEDICINES

Aluminium diacetate (not included in the National Licensed Medicines List of Afghanistan) is a topical astringent used as an antiseptic for various skin conditions including suppurating superficial wounds and tropical ulcers, and the lesions produced by impetigo and pemphigus.

13.5 MEDICINES AFFECTING SKIN DIFFERENTIATION AND PROLIFERATION

Acne vulgaris

Acne is a disorder of the pilosebaceous follicles and typically first appears during puberty when androgenic stimulation triggers excessive production of sebum. *Mild acne* is characterized by comedones and a few pustules, which heal without scarring, and usually responds to topical therapy alone. In *moderate acne*, where there are more extensive pustules causing mild scarring, oral antibiotics such as a tetracycline or erythromycin (Section 6.2.2) are commonly used. In *severe acne*, widespread pustules are accompanied by nodular abscesses and cysts, requiring systemic treatment with estrogens, anti-androgens, or retinoids. Since scarring of the skin resulting from severe nodular acne causes major distress, acne should always be treated as soon as possible. Exposure to substances suspected of causing or aggravating the condition should be avoided. Systemic treatment must be continued for several months before a response can be anticipated. During this time, topical preparations should be applied to the affected areas to prevent the development of new lesions.

Benzoyl peroxide is a keratolytic drug with bacteriostatic activity against *Propionibacterium acnes*; it is a component of many proprietary topical preparations for

the treatment of mild-to-moderate acne. Treatment is usually started at a lower strength and increased as tolerance develops to the initial irritant reaction. Preparations containing sulfur, which is bactericidal and promotes desquamation, are also often used, and may be combined with salicylic acid, which is a keratolytic agent.

Antibiotics, such as clindamycin, are widely used in a topical form to treat inflammatory acne. However, treatment must be maintained for 2–3 months before any benefit is seen and this prolonged course carries the risk of selection and spread of antibiotic-resistant organisms.

In mild-to-moderate acne, comedones and inflamed lesions respond well to benzoyl peroxide or to a topical retinoid.

Mild-to-moderate acne is generally treated with topical preparations. Systemic treatment with oral antibacterials is generally used for moderate-to-severe acne or where topical preparations are not tolerated or are ineffective or where application to the site is difficult.

Severe acne, acne unresponsive to prolonged courses of oral antibacterials, acne with scarring, or acne associated with psychological problems calls for early referral to a consultant dermatologist, who may prescribe isotretinoin for administration by mouth.

Oral administration of oxytetracycline or tetracycline 500 mg twice daily, or of erythromycin 500 mg twice daily, can be used; courses usually last 6–12 weeks and are repeated intermittently. Doxycycline 100 mg once daily can be used if oxytetracycline or tetracycline is inappropriate (for example, in renal impairment).

Topical tretinoin and its isomer, isotretinoin, are useful for treating comedones and inflammatory lesions in mild-to-moderate acne. These drugs are useful in treatment of acne in women aged 30–40 years, because acne in higher ages generally will not respond to antibacterial drugs. Isotretinoin is a toxic drug and should be used under supervision of

a specialist and should not be used during pregnancy. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop.

Psoriasis

Psoriasis, which affects people of all ages in all countries, and is one of the most common chronic dermatoses in industrialized countries, is characterized by epidermal thickening and scaling. Considerable local variations in its prevalence have been variously attributed to genetic, nutritional, and environmental factors. Various biological events may trigger psoriasis, such as streptococcal or viral infection, an emotional crisis, or pregnancy. Occasionally psoriasis may be provoked or exacerbated by drugs such as ACE inhibitors, beta-adrenoceptor antagonists (beta-blockers), chloroquine, lithium, and non-steroidal anti-inflammatory medicines.

Psoriasis vulgaris (chronic plaque psoriasis) is the most common form of the condition, usually affecting extensor surfaces of the limbs and the scalp. *Guttate psoriasis*, commonly seen in children, is often caused by a streptococcal infection; lesions may disappear following antimicrobial treatment. The condition is also known to resolve spontaneously but more commonly transforms into chronic plaque psoriasis. No treatment assures remission, but sunlight often clears lesions.

Emollients reduce dryness, scaling, and cracking, and may have an antiproliferative effect in psoriasis. They may be all that is necessary for mild psoriasis, and they are useful adjuncts to more specific treatments such as with **coal tar**, **dithranol**, and vitamin D analogues.

Dithranol restores the normal rate of epidermal cell proliferation and keratinization. Localized psoriasis vulgaris can frequently be cleared by daily applications for a period of 2–4 weeks. A short contact method of application causes little, if any, irritation or staining of normal skin, and is particularly useful for outpatient management. There is a risk of severe conjunctivitis if dithranol enters the eye.

Crude coal tar is also effective in the treatment of psoriasis. Some preparations also contain salicylic acid as a keratolytic. Good results are often obtained when daily applications or baths are combined with exposure to ultraviolet light or sunlight.

Topical corticosteroids have a limited role in psoriasis. A mild corticosteroid such as hydrocortisone may be used on the face and flexures, whereas a potent corticosteroid such as betamethasone is most appropriate for the scalp, hands, and feet. However, when extensive areas of the body surface are involved or when there is erythrodermic psoriasis, a sufficient amount may be absorbed to cause adrenal suppression; also, rebound often occurs after stopping treatment, resulting in a more unstable form of psoriasis.

Systemic treatment may be needed for severe, resistant, unstable, or complicated psoriasis; treatment should be initiated under specialist supervision. Systemic treatments include acitretin (not included in the Licensed Medicines List of Afghanistan), ciclosporin (Section 8.1), and methotrexate (Section 2.4).

Actinic keratosis

The lesions of actinic keratosis are distributed primarily over sun-exposed areas. Horny growths, which are often covered by light brown scales, are usually asymptomatic but can be disfiguring. They respond to light cautery and cryosurgery or topical application of **fluorouracil** over a 3-week period. Simple emollients may be satisfactory for people with many lesions.

Warts

Warts most commonly affect the hands, feet (plantar warts, verrucas), and anogenital region (condylomata acuminata); all are caused by the human papilloma virus. They may regress spontaneously at any time within months or years of their first appearance; however, particularly in immunosuppressed patients, they may spread and be difficult to cure. Many common, plane and plantar warts can reasonably be left untreated, but painful or unsightly lesions generally respond to application of topical preparations containing

salicylic acid. Where available, cryotherapy using liquid nitrogen applied with a cotton-tip or a spray is highly effective; however, freezing the skin can produce temporary or permanent depigmentation (particularly on dark skin), and should be used with caution.

Anogenital warts are usually transmitted by sexual contact; they should always be treated, although they frequently recur, because of the increased risk of cervical cancer.

Podophyllum resin, a caustic antimitotic agent, may be applied to small external lesions.

The risk of extensive local necrosis and systemic toxicity excludes the use of podophyllum resin on larger surfaces. When available, podophyllotoxin is a less toxic alternative. Where podophyllum is contraindicated or ineffective, surgical removal, electrocautery, cryosurgery, and laser therapy are possible options.

- **Benzoyl peroxide**

- **Dosage form**

- Cream: 5%
 - Topical lotion: 5% and 1%

- **Uses**

- Mild-to-moderate acne and as an adjunct to oral therapy in more severe cases

- **Precautions**

- Avoid contact with eyes, mouth, and mucous membranes
 - Avoid use of occlusive dressings
 - Avoid excessive exposure to sunlight

- **Administration**

Acne

- **ADULT and ADOLESCENT:** Initially apply directly to clean skin on alternate days, increasing frequency to 1–2 times daily as tolerance to irritant effect develops.
- **Adverse effects**
 - Initial irritation common but subsides with continued use (in some cases may need to reduce frequency of application or temporarily suspend use)
 - Rarely contact sensitivity occurs, and occasionally even one application can cause severe irritation.
 - May bleach fabrics, hair, and skin
- **Coal tar**
 - **Dosage form**
 - Topical lotion: 5%
 - Soap: 2%
 - Shampoo: 1%
 - **Use**
 - Chronic psoriasis, either alone or in combination with exposure to ultraviolet light
 - **Contraindications**
 - Inflamed, broken, or infected skin
 - **Not recommended under 6 years**
 - **Precaution**
 - Skin protection possibly required to reduce photosensitivity reactions
 - **Administration**

Psoriasis

- **ADULT and CHILD:** Apply directly to the affected area 1–3 times daily, preferably starting with lower-strength preparation, or add 100 ml to bath of tepid water and soak affected area for 10–20 minutes, once daily to once every 3 days for at least 10 baths. Bathing can be alternated with exposure to ultraviolet (UV) B rays, allowing at least 24 hours between exposure and treatment with coal tar.

- **Adverse effects**

- Irritation, photosensitivity reactions
- Rarely hypersensitivity
- Skin, hair, and fabrics discolored

- **Fluorouracil**

- **Dosage form**

- Topical ointment: 5%.

- **Uses**

- Premalignant and malignant skin conditions, including actinic keratosis
- Malignant disease (Section 8.2)

- **Contraindication**

- Hemorrhagic ulcerated tissue

- **Precautions**

- Avoid mucous membranes and eyes.
- Since ultraviolet light intensifies the inflammatory reaction, avoid prolonged exposure to sunlight.

- **Dose**

Premalignant and malignant skin conditions including actinic keratosis

- **ADULT:** Apply thinly to the affected area, 1–2 times daily until a marked inflammatory response occurs (usually 3–4 weeks); cover with occlusive dressing in malignant conditions; healing may require further 2 months after completion of treatment; maximum area of skin treated at one time, 500 cm².

Note: Avoid use of a metal applicator.

- **Adverse effects**

- Local inflammatory and allergic reactions
- Rarely erythema multiforme
- Photosensitivity reactions during and for up to 2 months after treatment

- **Salicylic acid**

- **Dosage form**

- Topical solution: 2%, 3%, and 5%

- **Uses**

- Hyperkeratotic conditions, including warts
- Adjunct in treatment of psoriasis, ringworm (Section 13.1)
- Seborrheic dermatitis (Section 13.3)
- Ichthyosis (Section 13.3)

- **Contraindications**

- 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.
- **Administration**
 - Hyperkeratotic skin disorders, including warts*
 - **ADULT** and **CHILD**: Apply directly to the affected area once daily, starting with lower-strength preparations; gradually increase strength until a satisfactory response is obtained.
 - Patient advice:*** Protect surrounding skin; rub warts gently with file or pumice stone once weekly.
- **Adverse effects**
 - Local irritation, dermatitis
 - Salicylism on excessive application or treatment of large areas, particularly in children

13.6 SCABICIDES AND PEDICULICIDES

Scabies

Scabies is caused by a mite, *Sarcoptes scabiei*, which burrows into the skin. It is readily transmitted from person to person, and therefore the entire household must be treated at the same time to prevent reinfection. Although it is not necessary to take a bath before treatment with an acaricide, all clothing and bedding should be washed to prevent reinfection.

Benzyl benzoate is an inexpensive scabicide. It must be applied to all skin surfaces, from the scalp to the soles of the feet, avoiding contact with the eyes; it is, however, too irritant for use on children. **Permethrin** is less irritant and, usually, more effective than benzyl

benzoate; it is also more expensive, but it may be used on children. Young infants can be treated with a cream containing precipitated sulfur, 6-10%, applied once daily for 1 week.

Pediculosis

Pediculosis of the head and body is caused by *Pediculus humanus capitis* and *Pediculus humanus corporis*, respectively; pubic lice (crab lice) infestations are caused by *Phthirus pubis*, which may also affect the eyelashes and brows. All are transmitted by person-to-person contact, and may also contaminate clothing and bedding. All members of the affected household (and sexual contacts) must be treated at the same time, and clothing and bedding should be washed or exposed to the air; in head lice infestations, hairbrushes and combs should also be disinfected.

Head and body lice are readily treated with **permethrin**; malathion is effective against pubic lice. **Benzyl benzoate** may be used for all lice infestations.

- **Benzyl benzoate**

Benzyl benzoate is a representative parasiticide. Various medicines can serve as alternatives.

- **Dosage form**

- Lotion: 25% in 60 ml bottle
- Powder

- **Uses**

- Scabies
- Head, body, and pubic lice

- **Precautions**

- Do not use on inflamed or broken skin.
- Avoid contact with eyes and mucous membranes.
- Not recommended for children

- Breast-feeding: Appendix C (withhold during treatment)

- **Administration**

Scabies

- **ADULT** and **CHILD**: Apply over whole body; repeat application without bathing on the following day and wash off 24 hours later; a third application may be needed in some cases.

Pediculosis

- **ADULT** and **CHILD**: Apply to the affected area and wash off 24 hours later; further applications possibly needed after 7 and 14 days.

- **Adverse effects**

- Local irritation, particularly in children

- **Lindane**

- **Dosage form**

- Topical shampoo: 1%

- **Use**

- Treatment of head and body lice and their eggs in patients who do not respond to other methods of treatment

- **Contraindications**

- Young children (their skin has more permeability and liver enzymes are not properly developed to metabolize lindane)
- Scabies and skin damage, psoriasis, atopic dermatitis (increases the absorption of drug)
- Patients with history of uncontrolled convulsions and patients allergic to the medicine

- **Precautions**
 - Avoid contact with eyes. In case of contact, wash eyes with water as soon as possible. Advise patient to see doctor if shampoo causes irritability of the eyes.
 - Do not use on injured and inflamed areas of the skins.
 - Breast-feeding: Appendix C (avoid breast-feeding during treatment)
- **Dosage and administration**
 - Most patients need only 30 ml of shampoo. Some patients may need 60 ml based on amount and length of the hair. Apply shampoo directly on hair without using water and wait for 4 minutes. Apply small amount of water on hair to produce foam. Wash out all foam immediately from hair. Avoid contact of foam with other parts of the body. Do not recommend more 60 ml for adult patients.
- **Adverse effects**
 - Neurological effects from confusion to convulsions have been reported when using lindane lotion. Although convulsions are associated with swallowing or misuse (including repeating the treatment), convulsion and death have also been reported from lindane shampoo use despite following instructions.
 - Irritant dermatitis is also reported.
- **Permethrin**
 - **Dosage form**
 - Topical cream: 5% in 30 g tube
 - Topical lotion: 1% in 60 ml bottle
 - **Uses**
 - Scabies

- Head and body lice
- **Precautions**
 - Do not use on inflamed or broken skin.
 - Avoid contact with eyes.
 - Breast-feeding: Appendix C (withhold during treatment)
- **Dose**

Scabies and body lice

- **ADULT** and **CHILD**: Apply cream over whole body and wash off after 8–12 hours; if hands, wash treated area with soap within 8 hours of application, treat the hands again; repeat application after 7 days.

Head lice

- **ADULT** and **CHILD**: Apply lotion to clean, damp hair and rinse off after 10 minutes.

- **Adverse effects**
 - Local irritation
 - Rarely rash and edema

SECTION 14: Diagnostic agents

LML strengths and dosage forms are marked in *italic* with an asterisk.

14.1 OPHTHALMIC MEDICINES

For general information on the use of eyedrops, *see* Section 21.

Fluorescein sodium is used in ocular diagnostic procedures and for locating areas of the cornea damaged due to injury or disease.

Tropicamide is a short-acting, relatively weak mydriatic that dilates the pupil and paralyzes the ciliary muscle. It facilitates the examination of the fundus of the eye.

- **Tropicamide**

Tropicamide is a representative mydriatic. Various medicines can serve as alternatives.

- **Dosage form**

- Eyedrops: 0.5% in 15 ml bottle and 1% in 3 ml bottle

- **Use**

- Dilation of the pupil to examine the fundus

- **Precautions**

- In hypermetropic (far-sighted) patients and patients aged over 60 years, may precipitate acute angle-closure glaucoma
- Darkly pigmented iris (more resistant to pupillary dilation; exercise caution to avoid overdosage)

- **Skilled tasks:** Advise patient not to perform skilled tasks (or example, operating machinery or driving) for 1–2 hours after mydriasis.
- **Administration**
 - Dilatation of pupil to examine the fundus, by ocular instillation*
 - **ADULT** and **CHILD:** 1 drop, 15–20 minutes before examination of the eye
- **Adverse effects**
 - Transient stinging and raised intraocular pressure
 - Local irritation, hyperemia, edema, and conjunctivitis (on prolonged administration)

14.2 RADIOCONTRAST MEDIA

Radiographic contrast media are needed for delineating soft tissue structures such as blood vessels, stomach, bowel loops, and body cavities that are not otherwise visualized by standard X-ray examination. The contrast media in this group, which all contain heavy atoms (metal or iodine), absorb a significantly different amount of X-rays than the surrounding soft tissue, thereby making the exposed structures visible on radiographs.

Barium sulfate is a metal salt that is used to delineate the gastrointestinal tract. It is not absorbed by the body and does not interfere with stomach or bowel secretion or produce misleading radiographic artifacts. Barium sulfate may be used in either single- or double-contrast techniques or computer-assisted axial tomography. In double-contrast examinations, gas is introduced into the gastrointestinal tract by using suspensions of barium sulfate containing carbon dioxide or by using separate gas-producing preparations based on sodium bicarbonate. Air administered through a gastrointestinal tube can be used as an alternative to carbon dioxide to achieve a double-contrast effect.

Amidotrizoates (meglumine amidotrizoate and sodium amidotrizoate) are iodinated ionic monomeric organic compounds. Although both salts have been used alone in diagnostic radiography (including computer-assisted axial tomography), a mixture of both is often preferred so as to minimize adverse effects and to improve the quality of the examination. Amidotrizoates are used in a wide range of procedures, including urography, and examination of the gallbladder, biliary ducts, and spleen. Owing to their high osmolality, they are associated with a high incidence of adverse effects. The osmolality for a given radiodensity, which depends on iodine concentration, can be reduced by using an ionic dimeric medium such as **meglumine iotroxate**, which contains twice the number of iodine atoms in a molecule, or by using a non-ionic medium such as **iohexol**. Low osmolality radiocontrast media such as iohexol are associated with a reduction in some adverse effects (*see below*), but they are generally more expensive. Iohexol is used for a wide range of diagnostic procedures, including urography, angiography, and arthrography, and also in computer-assisted axial tomography. Meglumine iotroxate is excreted into the bile after intravenous administration and is used for cholecystography and cholangiography.

Iopanoic acid is an organic compound containing iodine taken by mouth. This compound is readily absorbed in the gastrointestinal tract and excreted into bile and gathered in gallbladder, thus making the gallbladder ready for cholecystography. Propylidone is another organic compound containing iodine, which is used for bronchography.

Hypersensitivity

Anaphylactoid reactions to iodinated radiocontrast media are more common with ionic, high-osmolality compounds. Patients with a history of asthma or allergy, drug hypersensitivity, adrenal suppression, heart disease, previous reaction to contrast media, and those receiving beta-adrenoceptor antagonists (beta-blockers) are at increased risk. Non-ionic media are preferred for these patients and beta-blockers should be discontinued if possible.

- **Amidotrizoate (diatrizoic acid)**

Meglumine amidotrizoate and sodium amidotrizoate are representative iodinated ionic monomeric radiocontrast media. Various media can serve as alternatives.

- **Dosage form**

- Iodinated injection: 140 mg, 240 mg, 370 mg, and 420 mg (as sodium or meglumine salt)/ml in 20 ml ampoule
- Injection solution: Diatrizoic acid meglumine 66% + diatrizoic acid sodium 10% (also known as Urografin)

- **Uses**

- Urography, venography, operative cholangiography, splenoportography, arthrography, discography
- Computer-assisted axial tomography

- **Contraindication**

- Hypersensitivity to iodine-containing compounds

- **Precautions**

- History of allergy, atopy, or asthma
- Severe hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Dehydration (correct fluid and electrolyte balance before administration)
- Multiple myeloma (risk of fatal renal failure if dehydrated)
- Cardiac disease, hypertension, pheochromocytoma, sickle-cell disease, hyperthyroidism, the elderly, debilitated patients, and children (increased risk of adverse effects)
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- May interfere with thyroid function tests

- Concomitant use of biguanides (withdraw 48 hours before administration; restart when renal function stabilized)
- ***Important note:* Because of the risk of hypersensitivity reactions, adequate resuscitation facilities must be immediately available when radiographic procedures are carried out.**

○ **Dose**

Diagnostic radiography

- **ADULT** and **CHILD:** Route of administration and dosage depend on procedure and preparation used (consult manufacturer's literature).

Administration: By specialist radiographers only, according to manufacturer's directions

○ **Adverse effects**

- Nausea, vomiting, diarrhea, metallic taste, flushing, sensations of heat, weakness, dizziness, headache, cough, rhinitis, sweating, sneezing, lacrimation, visual disturbances, pruritus, salivary gland enlargement, pallor, cardiac disorders, hemodynamic disturbances, and hypotension
- Disseminated intravascular coagulation
- Fibrinolysis and depression of blood coagulation factors
- Rarely nephrotoxicity, convulsions, paralysis, coma, rigors, arrhythmias, pulmonary edema, circulatory failure, and cardiac arrest
- Occasionally anaphylactoid or hypersensitivity reactions
- Hyperthyroidism
- Pain on injection
- Extravasation may result in tissue damage, thrombophlebitis, thrombosis, venospasm, and embolism.

- **Barium sulfate**

- **Dosage form**

- Parenteral aqueous solution: 30%
 - Oral suspension powder: 135 g/pack and 1 kg /pack

- **Use**

- Radiographic examination of the gastrointestinal tract (*see also* notes above)

- **Contraindications**

- Intestinal obstruction, and/or conditions such as pyloric stenosis or lesions that predispose to obstruction
 - Intestinal perforation or conditions with risk of perforation, such as acute ulcerative colitis, diverticulitis, or after rectal or colonic biopsy, sigmoidoscopy, or radiotherapy

- **Precaution**

- Maintain adequate hydration after procedure to prevent severe constipation.

- **Dose**

- Radiographic examination of the gastrointestinal tract*

- **ADULT** and **CHILD:** Route of administration and dosage depend on procedure and preparation used (consult manufacturer's literature).

- Administration:** Only by specialist radiographers, according to manufacturer's directions*

- **Adverse effects**

- Constipation or diarrhea, gastrointestinal obstruction, appendicitis, abdominal cramps, and bleeding
- Perforation of bowel resulting in peritonitis, adhesions, granulomas, and high mortality rate
- Electrocardiographical changes (with rectal administration)
- Pneumonitis or granuloma formation (following accidental aspiration into lungs)

SECTION 15: Disinfectants and antiseptics

LML strengths and dosage forms are marked in italic with an asterisk.

15.1 ANTISEPTICS

An antiseptic is a type of disinfectant that destroys or inhibits growth of microorganisms on living tissues without causing harm when applied to surfaces of the body or to exposed tissues. Some antiseptics can be applied to the unbroken skin or mucous membranes, to burns, and to open wounds to prevent sepsis by removing or excluding microbes from these areas.

Iodine has been modified for use as an antiseptic. The iodophore **polyvidone-iodine** is effective against bacteria, fungi, viruses, protozoa, cysts, and spores, and significantly reduces surgical wound infections. The solution of polyvidone-iodine releases iodine on contact with the skin.

Chlorhexidine has a wide spectrum of bactericidal and bacteriostatic activity and is effective against both gram-positive and gram-negative bacteria, although it is less effective against some species of *Pseudomonas* and *Proteus* and is relatively inactive against mycobacteria. It is not active against bacterial spores at room temperature. Chlorhexidine is incompatible with soaps and other anionic materials, such as bicarbonates, chlorides, and phosphates, forming salts of low solubility, which may precipitate out of solution.

Ethanol has bactericidal activity and is used to disinfect skin prior to injection, venipuncture, or surgical procedures. It is also used to disinfect hands and to clean surfaces.

15.2 DISINFECTANTS

A disinfectant is a chemical agent that destroys or inhibits growth of pathogenic microorganisms in the non-sporing or vegetative state. Disinfectants do not necessarily kill all organisms but reduce them to a level that does not harm health or the quality of perishable goods. Disinfectants are applied to inanimate objects and materials such as instruments and surfaces to control and prevent infection. They may also be used to disinfect skin and other tissues prior to surgery (*see also* Section 15.1, Antiseptics).

Disinfection of water can be achieved by either physical or chemical means. Physical methods include boiling, filtration, and ultraviolet irradiation. Chemical methods include the use of **chlorine-releasing compounds**, such as sodium hypochlorite, tosylchloramide sodium (chloramine), halazone, and sodium dichloroisocyanurate. Where water is not disinfected at source, it may be disinfected by boiling or by chemical means for drinking, cleaning teeth, and food preparation.

Chlorine is a hazardous substance. It is highly corrosive in concentrated solution and splashes can cause burns and damage the eyes. Appropriate precautions must be taken when concentrated chlorine solutions or powders are handled.

The chlorinated phenolic compound **chloroxylonol** is effective against a wide range of gram-positive bacteria. It is less effective against staphylococci and gram-negative bacteria; it is often ineffective against *Pseudomonas* spp. and it is inactive against spores.

The aldehyde bactericidal disinfectant **glutaral** is rapidly effective against both gram-positive and gram-negative bacteria. It is active against the tuberculosis bacillus, fungi such as *Candida albicans*, and viruses such as HIV and hepatitis B; it is slowly effective against bacterial spores. A 2% w/v aqueous alkaline glutaral solution (buffered to pH 8) can be used to sterilize heat-sensitive pre-cleansed instruments and other equipment.

- **Cetrimide + chlorhexidine gluconate**
 - **Dosage form**
 - Concentrated antiseptic solution for topical use: 15% cetrimide and 1.5% chlorhexidine
 - **Uses**
 - Prevention of skin infections, disinfection of medical equipment
 - **Contraindications**
 - Sensitivity to the combination of cetrimide and chlorhexidine
 - **Precautions**
 - Avoid contact with eyes, meninges (membranes surrounding the brain and spinal cord), and ears
 - **Dilution dose**
 - This medicine must be diluted before use. The 1% solution (1 ml concentrated solution in 100 ml of water) is used for disinfection of ulcers and burns, disinfection of metal equipment if sterilization facility is not available (should be in contact with solution for 30 minutes), and disinfection of equipment, furniture, and other objects used by the patient.
 - 3.3% solution (1 ml concentrated solution in 30 ml water) is used to disinfect ulcers and burns, which require the use of higher-concentration antiseptic.
 - 3.3% solution (1 ml concentrated solution in 30 ml of 70% alcohol) is used for immediate disinfection of skin before surgical operation and other invasive procedures, and disinfection of clean equipment (in contact with solution for at least 2 minutes). (Do not place endoscopic equipment in the solution.)

Note: The aqueous solutions need to be autoclaved in 121°C temperature for 15 minutes. Syringes, needles, and other equipment disinfected with this solution needs to be washed with distilled water or normal saline (physiologic solution).

- **Adverse effects**

- Some very rare side effects reported, including severe allergic reaction that causes difficulty in breathing, weakness, collapse and death, and sometimes begins with swelling of the lips, tongue, face, and skin lesions.
- Other possible adverse effects include allergic skin disorders such as dermatitis, itching, skin redness, eczema, desquamation, skin lesions, skin irritations, and blisters.
- Dryness of the skin and chemical burns with continuous use of the drug have been rarely reported.

- **Chlorhexidine**

- **Dosage form**

- Gel: 7.5% (digluconate)
- Topical solution: 5% and 7.1% (digluconate) for dilution

- **Uses**

- Antiseptic
- Disinfection of clean instruments
- Care of umbilical cord infections

- **Precautions**

- Aqueous solutions (which are susceptible to microbial contamination) should be freshly prepared.
- Appropriate measures required to prevent 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)
- Alcohol-based solutions are flammable.

○ **Administration**

Antiseptic (preoperative skin disinfection and hand washing)

- **ADULT** and **CHILD**: Use 0.5% solution in alcohol (70%) or 2% or 4% detergent solution to the skin area.

Antiseptic (wounds, burns, and other skin damage)

- **ADULT** and **CHILD**: Apply 0.05% aqueous solution directly to the affected area.

Prevention of umbilical cord infections

- Apply 7.1% solution directly to the affected area.

Disinfection of clean instruments

- Immerse for at least 30 minutes in 0.05% solution containing sodium nitrite 0.1% (to inhibit metal corrosion).

Emergency disinfection of clean instruments

- Immerse for 2 minutes in 0.5% solution in alcohol (70%).

Dilution and administration: According to manufacturer's directions

- **Adverse effects**
 - Occasional skin sensitivity and irritation

- **Hydrogen peroxide**

- **Dosage form**
 - Topical solution: 6% (20 vols)
 - Mouthwash solution: 6% (20 vols)
 - Pure solution: 30% (100 vols)

Note: High-concentration solutions of hydrogen peroxide (30%) are used only for preparing diluted solutions.

- **Uses**
 - For skin disinfection, particularly cleansing and deodorizing wounds and ulcers
 - Oral hygiene: Mouthwashes containing an oxidizing agent such as hydrogen peroxide may be useful in the treatment of acute ulcerative gingivitis, since the organisms involved are anaerobes. It also has a mechanical cleansing effect arising from frothing when in contact with oral debris.
- **Precautions**
 - Large or deep wounds
 - Avoid on healthy skin and near eyes.
 - Incompatible with products containing iodine or potassium permanganate
- **Administration**

Superficial bacterial skin infection

- Apply 2–3 times daily for up to 3 weeks.

Oral hygiene

- Rinse the mouth for 2–3 minutes with 15 ml diluted in half a tablespoon of warm water 2–3 times daily.

- **Adverse effects**

- Inflammation and irritation of skin and mucus membranes especially, with highly concentrated solutions
- Local irritation
- Rarely taste disorder and local anesthesia
- Hypertrophy of papillae of tongue in prolonged use

- **Glycerin boric (glycerin + boric acid)**

A strong antiseptic used primarily for the treatment of mouth, teeth, and ear disorders.

- **Dosage form**

- Topical solution and otic liquid: 5% glycerine boric used topically in the ear as ceruminolytic

- **Uses**

- As an antiseptic of mouth cavity and teeth
- Solutions and drops are used in the treatment of ear and skin disorders.
- Glycerin alone has hygroscopic properties that attract moisture from the environment and causes cerumin to soften.
- Boric acid is used for its antifungal and antibacterial properties.

- **Povidone-iodine**

Also known as polyvidone-iodine

- **Dosage form**

- Topical solution: 7.5% and 10%
- Vaginal gel: 10% in 18 g tube
- **Uses**
 - Antiseptic
 - Skin disinfection
- **Contraindications**
 - Avoid regular or prolonged use in patients with thyroid disorders or those taking lithium.
 - Avoid regular use in neonates.
 - Avoid in very low-birth-weight infants.
- **Precautions**
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Broken skin (*see below*)
 - Renal impairment: Appendix D
 - ***Large open wounds:*** The application of povidone-iodine to large wounds or severe burns may produce systemic adverse effects such as metabolic acidosis, hypernatremia, and impairment of renal function.
- **Administration**

Pre- and postoperative skin disinfection

- **ADULT and CHILD:** Apply undiluted solution to the skin area.

Antiseptic (minor wounds and burns)

- **ADULT and CHILD:** Apply undiluted solution to the affected area, twice daily (*see also* Precautions).

- **Adverse effects**

- Irritation of skin and mucous membranes
- May interfere with thyroid function tests
- Systemic effects (*see under* Precautions)

- **Sodium hypochlorite (chlorine)**

- **Dosage form**

- Topical solution: 0.5% and 5%

- **Uses**

- Disinfection of surfaces, medical equipment, and water

- **Contraindications**

- Avoid exposure of product to flame.
- Activity diminished in presence of organic material and increasing pH (can cause release of toxic chlorine gas)

- **Administration**

Surface disinfection (minor contamination)

- Apply 0.1% solution.

Instrument disinfection

- Soak in (0.1%) solution for a minimum of 15 minutes (to avoid corrosion do not soak for more than 30 minutes).
- Rinse with sterile water.

Dilution and administration: According to manufacturer's directions

- **Adverse effects**

- Irritation and burning sensation on skin

SECTION 16: Diuretics

Diuretics increase urinary excretion of water and electrolytes, and are therefore used to relieve edema associated with heart failure, nephrotic syndrome, or hepatic cirrhosis. Some diuretics are used at lower doses to reduce raised blood pressure. Osmotic diuretics are mainly used to treat cerebral edema, and also to lower raised intraocular pressure.

Most diuretics increase urine volume by inhibiting the reabsorption of sodium and chloride ions in the renal tubule; they also modify renal handling of potassium, calcium, magnesium, and urate. Osmotic diuretics act differently; they cause an increase in urine volume by an osmotic effect.

Although loop diuretics are the most potent, their duration of action is relatively short; thiazide diuretics are moderately potent but produce diuresis for a longer period. Potassium-sparing diuretics have a relatively weak diuretic effect. Carbonic anhydrase inhibitors are weak diuretics and are rarely used for their diuretic effect but are principally used to lower intraocular pressure in glaucoma (Section 21.4).

LOOP DIURETICS

Loop diuretics, or high-ceiling diuretics, such as **furosemide**, rapidly produce an intense dose-dependent diuresis of relatively short duration. Oral furosemide produces diuresis within 30–60 minutes of administration, and a maximum diuretic effect in 1–2 hours. The diuretic action lasts for 4–6 hours. Intravenous furosemide produces diuresis within 5 minutes, and a maximum diuretic effect in 20–60 minutes; diuresis is complete within 2 hours.

Loop diuretics inhibit reabsorption of sodium and chloride ions from the ascending loop of Henlé in the renal tubule and are useful particularly in situations where rapid and effective diuresis is needed: for example, in acute pulmonary edema due to left ventricular failure (*see* Section 12.4). They are also used to treat edema associated with renal and hepatic disorders, and in high doses are used in the management of oliguria due

to chronic renal insufficiency. Loop diuretics may be effective in patients who are unresponsive to thiazide diuretics.

Because of their shorter duration of action, the risk of *hypokalemia* may be lower with loop diuretics than with thiazide diuretics; if required, a potassium-sparing diuretic may be given as an adjunct to prevent hypokalemia. Loop diuretics may cause *hypovolemia* and excessive use can produce severe dehydration, with the possibility of circulatory collapse. Furosemide may cause *hyperuricemia* and precipitate attacks of gout. Rapid high-dose injection or infusion of furosemide may cause tinnitus and even permanent deafness.

THIAZIDE DIURETICS

Thiazide diuretics, such as **hydrochlorothiazide**, are moderately potent and act by inhibiting sodium and chloride ion reabsorption at the beginning of the distal convoluted tubule. They produce diuresis within 1–2 hours of oral administration and most have a duration of action of 12–24 hours.

Thiazide diuretics are used in the management of edema associated with mild-to-moderate congestive heart failure, renal dysfunction, or hepatic disease; however, thiazides are not effective in patients with poor renal function (that is, a creatinine clearance of less than 30 mL/min). In severe fluid retention, a loop diuretic may be necessary.

In hypertension, a thiazide diuretic is used at a low dose to lower blood pressure with very little biochemical disturbance; the maximum therapeutic effect may not be seen for several weeks. Higher doses should **not** be used because they do not necessarily increase the hypotensive response but may cause marked changes in plasma potassium, sodium, magnesium, uric acid, glucose, and lipids. If a thiazide alone does not lower blood pressure adequately, it may be combined with another antihypertensive drug, such as a beta-adrenoceptor antagonist (Section 12.3).

Urinary excretion of calcium is reduced by thiazide diuretics, and this property is occasionally of value in the treatment of idiopathic hypercalciuria in patients with calcium-containing calculi. Paradoxically, thiazide diuretics are used in the treatment of diabetes insipidus, since in this disease they reduce urine volume.

Thiazide diuretics, especially in high doses, produce a marked increase in potassium excretion that may cause hypokalemia; this is dangerous in patients with severe coronary artery disease and those being treated with cardiac glycosides. In hepatic failure, hypokalemia can precipitate encephalopathy, particularly in alcoholic cirrhosis. Potassium-sparing diuretics are an effective alternative to potassium supplements for prevention of hypokalemia induced by thiazide diuretics; however, supplementation with potassium in any form is seldom necessary with the smaller doses of diuretics used to treat hypertension.

POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics include **amiloride** and **spironolactone**; they are weak diuretics that reduce potassium excretion and increase sodium excretion in the distal tubule. Amiloride takes effect about 2 hours after oral administration, reaches its peak diuretic action in 6–10 hours, and persists for about 24 hours. Spironolactone, which acts by antagonizing aldosterone, has a relatively slow onset of action, requiring 2–3 days to achieve maximum diuretic effect and a similar period to cease its action after discontinuation of treatment.

Amiloride may be used alone; but its principal use is in combination with a thiazide or a loop diuretic to conserve potassium during treatment of congestive heart failure or hepatic cirrhosis with ascites.

Spironolactone is used in the treatment of refractory edema due to heart failure, hepatic cirrhosis (with or without ascites), nephrotic syndrome, and ascites associated with malignancy. It is frequently given with a thiazide or a loop diuretic, helping to conserve potassium in those at risk from *hypokalemia*. A low dose of spironolactone is beneficial

in severe heart failure in patients who are already taking an ACE inhibitor and a diuretic. Spironolactone is used in the diagnosis and treatment of primary hyperaldosteronism; presumptive evidence for diagnosis is provided by correction of hypokalemia and of hypertension.

The most dangerous adverse effect of potassium-sparing diuretics, such as amiloride or spironolactone, is *hyperkalemia*, which can be life-threatening. These diuretics are thus best avoided, or used with extreme caution, in patients who have or may develop hyperkalemia, such as those with renal failure, patients receiving other potassium-sparing diuretics, and patients taking ACE inhibitors or potassium supplements.

ELECTROLYTE IMBALANCE

The adverse effects of diuretic therapy are mainly due to the fluid and electrolyte imbalance induced by the drugs. *Hyponatremia* is an adverse effect of all diuretics. The risk of *hypokalemia*, which may occur with both thiazide and loop diuretics, depends more on the duration of action than on potency and is thus greater with thiazides than with loop diuretics (when given in equipotent doses). Potassium-sparing diuretics can cause *hyperkalemia*. Other electrolyte disturbances include *hypercalcemia* (thiazides), *hypocalcemia* (loop diuretics), and *hypomagnesemia* (thiazide and loop diuretics).

Symptoms of fluid and electrolyte imbalance include dry mouth, thirst, gastrointestinal disturbances (including nausea and vomiting), weakness, lethargy, drowsiness, restlessness, seizures, confusion, headache, muscle pains or cramps, hypotension (including postural hypotension), oliguria, and arrhythmias.

Elderly

The elderly are more susceptible to electrolyte imbalance than younger patients. Treatment should begin with a lower initial dose of the diuretic (commonly about 50% of the full recommended adult dose) and then adjusted carefully according to renal function, plasma electrolytes, and diuretic response.

OSMOTIC DIURETICS

Osmotic diuretics, such as mannitol, are administered in sufficiently large doses to raise the osmolarity of plasma and renal tubular fluid. Osmotic diuretics are used to reduce or prevent cerebral edema, to reduce raised intraocular pressure, and to treat disequilibrium syndrome. Mannitol is also used to control intraocular pressure during acute attacks of glaucoma. Reduction of cerebrospinal and intraocular fluid pressure occurs within 15 minutes of the start of infusion and lasts for 3–8 hours after the infusion has been discontinued; diuresis occurs after 1–3 hours. Circulatory overload due to expansion of extracellular fluid is a serious adverse effect of mannitol; as a consequence, pulmonary edema can be precipitated in patients with diminished cardiac reserve, and acute water intoxication may occur in patients with inadequate urine flow.

LML strengths and dosage forms are marked in *italic* with an asterisk.

- **Furosemide**

Furosemide is a representative loop diuretic. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 20 mg and 40 mg
- Injection: 10 mg/ml in 2 ml ampoule

- **Uses**

- Edema
- Oliguria due to renal failure
- Heart failure (Section 12.4)

- **Contraindications**

- Renal failure with anuria

- Precomatose states associated with liver cirrhosis
- **Precautions**
 - Monitor electrolytes, particularly potassium and sodium
 - Hypotension
 - Elderly (reduce dose)
 - Pregnancy: Appendix B
 - In oliguria, correct hypovolemia before administration
 - Renal impairment: Appendix D
 - Hepatic impairment: Appendix E
 - Prostatic enlargement
 - **Interactions:** Appendix A

○ **Dose**

Edema, by mouth

- **ADULT:** Initially 40 mg daily on rising; usual maintenance dose, 20–40 mg daily; may be increased to 80 mg daily or more in resistant edema
- **CHILD:** 1–3 mg/kg daily (max. 40 mg daily)

Acute pulmonary edema, by slow intravenous injection

- **ADULT:** 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 intravenous infusion at a rate not exceeding 4 mg/min
- **CHILD:** 0.5–1.5 mg/kg daily (max. 20 mg daily)

Oliguria (glomerular filtration rate less than 20 ml/min), by slow intravenous infusion at a rate not exceeding 4 mg/min

- **ADULT:** 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; 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; the effective dose (up to 1 g) can be repeated every 24 hours.

Note: Dose to be diluted in a suitable amount of infusion fluid, according to the hydration of the patient

- **Adverse effects**

- Hypokalemia, hypomagnesemia, hyponatremia, hypochloremic alkalosis (for symptoms of fluid and electrolyte imbalance, *see* introductory notes), increased calcium excretion, hypovolemia, hyperglycemia (but less often than with thiazide diuretics)
- Temporary increase in plasma cholesterol and triglyceride concentration
- Less commonly hyperuricemia and gout
- Rarely rash, photosensitivity, bone marrow depression (**withdraw treatment**), pancreatitis (with large parenteral doses), tinnitus and deafness (with rapid administration of large parenteral doses and in renal impairment)
- Deafness may be permanent if other ototoxic drugs are taken.

- **Hydrochlorothiazide**

Hydrochlorothiazide is a representative thiazide diuretic. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 25 mg and 50 mg

- **Uses**

- Edema
- Diabetes insipidus

- Mild hypertension alone, moderate-to-severe hypertension in combination with other drugs (Section 12.3)
- Heart failure (Section 12.4)
- **Contraindications**
 - Severe renal or severe hepatic impairment
 - Hyponatremia, hypercalcemia, refractory hypokalemia, symptomatic hyperuricemia
 - Addison's disease
- **Precautions**
 - Renal impairment: Appendix D
 - Hepatic impairment: Appendix E
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Elderly
 - Electrolytes may need to be monitored with high doses or in renal impairment.
 - May aggravate diabetes mellitus and gout
 - May exacerbate systemic lupus erythematosus
 - Porphyria
 - **Interactions:** Appendix A
- **Dose**

Edema, by mouth

- **ADULT:** Initially 25 mg daily on rising (reduce to 12.5 mg daily in the elderly), increased to 50 mg daily if necessary

Severe edema in patients unable to tolerate loop diuretics, by mouth

- **ADULT:** Up to 100 mg either daily or on alternate days (max. 100 mg daily)

Nephrogenic diabetes insipidus, by mouth

- **ADULT:** Initially up to 100 mg daily

- **Adverse effects**

- Hypokalemia, hypomagnesemia, hyponatremia, hypochloremic alkalosis (for symptoms of fluid and electrolyte imbalance see introductory notes)
- Hypercalcemia
- Hyperglycemia
- Hyperuricemia, gout
- Rash, photosensitivity
- Altered plasma lipid concentration
- Rarely impotence (reversible), blood disorders including neutropenia and thrombocytopenia
- Pancreatitis, intrahepatic cholestasis
- Hypersensitivity reactions including pneumonitis, pulmonary edema, and severe skin reactions
- Acute renal failure

- **Mannitol**

- **Dosage form**

- Injectable solution: 10% and 20% in 100 ml bottle; 10% and 20% in 500 ml bottle

- **Uses**

- Cerebral edema
- Raised intraocular pressure (emergency treatment or before surgery)

- **Contraindications**
 - Pulmonary edema
 - Intracranial bleeding (except during craniotomy)
 - Severe congestive heart failure
 - Metabolic edema with abnormal capillary fragility
 - Severe dehydration
 - Renal failure (unless test dose produces diuresis)
- **Precautions**
 - Monitor fluid and electrolyte balance
 - Monitor renal function
- **Dose**

Test dose (if patient is oliguric or if renal function is inadequate), by intravenous infusion as a 20% solution infused over 3–5 minutes

- **ADULT and CHILD:** 200 mg/kg; repeat test dose if urine output is less than 30–50 ml/hour; if response is inadequate after a second test dose, reevaluate the patient.

Raised intracranial or intraocular pressure, by intravenous infusion as a 20% solution infused over 30–60 minutes

- **ADULT:** 0.25–2 g/kg
- **CHILD:** 0.5–1.5 g/kg

Cerebral edema, by intravenous infusion as a 20% solution infused rapidly

- **ADULT and CHILD:** 1 g/kg

Pharmaceutical precautions: Solutions containing mannitol with a dosage form exceeding 15%, may crystallize during storage. Crystals must be

redissolved by warming solutions before use, and solutions must not be used if any crystals remain; intravenous administration sets must have a filter. Mannitol should not be administered with whole blood or passed through the same transfusion set as blood.

- **Adverse effects**

- Fluid and electrolyte imbalance (for symptoms, *see* introductory notes above)
- Circulatory overload, acidosis
- Pulmonary edema (particularly in diminished cardiac reserve)
- Chills, fever, chest pain, dizziness, visual disturbances
- Hypotension or hypertension
- Urticaria, hypersensitivity reactions
- Extravasation may cause edema, skin necrosis, and thrombophlebitis
- Rarely acute renal failure (with large doses)

- **Spironolactone**

- **Dosage form**

- Tablets: 25 mg, 50 mg, and 100 mg

- **Uses**

- Refractory edema in congestive heart failure
- Adjunct to ACE inhibitor and a loop or thiazide diuretic in severe congestive heart failure
- Nephrotic syndrome
- Hepatic cirrhosis with ascites and edema
- Ascites associated with malignancy
- Primary hyperaldosteronism

- **Contraindications**

- Hyperkalemia

- Hyponatremia
- Moderate renal impairment
- Addison's disease

○ **Precautions**

- Monitor blood urea nitrogen and plasma electrolytes (discontinue if hyperkalemia)
- Elderly (reduce dose)
- Diabetes mellitus
- Renal impairment: Appendix D
- Hepatic impairment: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Porphyria
- High doses carcinogenic in rodents
- **Interactions:** Appendix A

○ **Dose**

Edema, by mouth

- **ADULT:** 100–200 mg daily, increased if necessary to 400 mg daily in resistant edema; usual maintenance dose, 25–200 mg daily
- **CHILD:** Initially 1–3 mg/kg daily in 1–2 divided doses

Primary hyperaldosteronism, by mouth

- **ADULT:** 400 mg daily for 3–4 weeks (*see note above*)

Preoperative management

- **ADULT:** 100–400 mg daily; if not suitable for surgery, give lowest effective dose for long-term maintenance.

Adjunct in severe heart failure, by mouth

- **ADULT:** Usually 25 mg daily

Adjunct in severe heart failure, by mouth

- **ADULT:** Usually 25 mg daily

○ **Adverse effects**

- Hyperkalemia, hyponatremia, hyperchloremic acidosis, dehydration (for symptoms of fluid and electrolyte imbalance, see introductory notes above)
- Transient increase in blood urea nitrogen
- Diarrhea
- Gynecomastia, menstrual irregularities
- Impotence, hirsutism, deepening of voice
- Rash, ataxia, fever, hepatotoxicity

SECTION 17: Gastrointestinal medicines

LML strengths and dosage forms are marked in italic with an asterisk.

17.1 ANTACIDS AND OTHER ANTI-ULCER MEDICINES

Antacids (which usually contain aluminium or magnesium compounds) can often relieve symptoms in ulcer dyspepsia and in non-erosive gastro-esophageal reflux; they are also sometimes used in functional (non-ulcer) dyspepsia but the evidence of benefit is uncertain. Antacids are best given when symptoms occur or are expected, usually between meals and at bedtime, 4 or more times daily; additional doses may be required up to once an hour. Conventional doses, for example, 10 ml 3 or 4 times daily of liquid magnesium-aluminium antacids promote ulcer healing, but less well than antisecretory drugs (such as an H₂-receptor antagonist); proof of a relationship between healing and neutralizing capacity is lacking. Liquid preparations are more effective than solids.

Aluminium- and magnesium-containing antacids (for example, **aluminium hydroxide** and **magnesium hydroxide**), being relatively insoluble in water, are long-acting if retained in the stomach. They are suitable antacids for most purposes. Magnesium-containing antacids have a laxative effect whereas aluminium-containing antacids may be constipating.

H₂-receptor antagonists (for example, ranitidine) heal gastric and duodenal ulcers by reducing the secretion of gastric acid as a result of histamine H₂-receptor blockade; they can also relieve gastro-esophageal reflux disease. High doses of H₂-receptor antagonists have been used in Zollinger-Ellison syndrome, but a proton-pump inhibitor is now preferred.

Maintenance treatment with low doses of H₂-receptor antagonists has largely been replaced in *Helicobacter pylori*-positive patients by eradication regimens (see below). Maintenance treatment may occasionally be used for those with frequent severe recurrences and for elderly patients who suffer ulcer complications.

Treatment of undiagnosed dyspepsia with H₂-receptor antagonists may be acceptable in younger patients but care is required in older people because their symptoms may be caused by gastric cancer.

H₂-receptor antagonist therapy can promote healing of NSAID-associated ulcers (particularly duodenal). Treatment also reduces the risk of acid aspiration in obstetric patients at delivery (Mendelson's syndrome).

Peptic ulcer

Peptic ulceration involves the stomach, duodenum, and lower esophagus. General and inexpensive measures, such as introducing a healthy lifestyle, stopping smoking, and taking antacids, can promote healing, but relapse is common. The possibility of malignant disease should be considered in all patients over the age of 40 years who are suspected of having an ulcer.

Gastric and duodenal ulcers are healed by 4–8 weeks of treatment with H₂-receptor antagonists but there is a high rate of relapse (greater than 70% over 2 years), requiring maintenance therapy. Relapses can be prevented very successfully by eradicating *Helicobacter pylori*, which is causally associated with most peptic ulcers (except those related to NSAID use). Eradication of *H. pylori* reduces the relapse rate to about 4–8%. This is undoubtedly a cost-effective option when compared with the alternatives of long-term maintenance therapy with low-dose H₂-receptor antagonists or repeated treatment of recurrent ulcers. It is recommended that the presence of *H. pylori* is confirmed before starting eradication treatment, particularly for gastric ulcers. The urea breath test is used widely to test for *H. pylori*, but false-negative results may occur if used soon after administration of either a proton-pump inhibitor or an antibacterial. Eradication regimens are based on a combination of an acid-reducing (“antisecretory”) drugs and antibacterials.

The following model eradication regimen is suggested on the basis of its efficacy and simplicity (doses suitable for adults are shown):

- Omeprazole 40 mg daily for 1 week, *plus* metronidazole 400 mg 3 times daily for 1 week, *plus* amoxicilline 500 mg 3 times daily for 1 week

or

- Lansoprazole 30 mg daily for 1 week, *plus* clarithromycin 500 mg 2 times daily for 1 week, *plus* amoxicilline 1 g two times daily for 1 week

The choice of eradication regimen for a particular country should take into account local resistance to antibacterials, as well as the cost and availability of the necessary drugs.

NSAIM-associated ulcers

Gastrointestinal bleeding and ulceration may occur with NSAIM use. To avoid this, use of the NSAIM should be stopped, but this is not always possible. A proton-pump inhibitor or an H2-receptor antagonist at twice the usual dose may be considered for protection against NSAIM-associated gastric and duodenal ulcers.

Patients who must continue NSAIM therapy after ulcer development may take high-dose H2-receptor antagonists concomitantly, but ulcers tend to heal more slowly with H2-receptor antagonists if NSAIMs are continued. A proton-pump inhibitor, such as omeprazole, is more effective but more expensive.

In patients who can discontinue NSAIM therapy after ulcer development, treatment with an H2-receptor antagonist is effective, but a treatment period of up to 8 weeks may be necessary. A proton-pump inhibitor usually produces the most rapid healing. After healing, continued prophylaxis is required.

Dyspepsia

Dyspepsia covers pain, fullness, early satiety, bloating, and nausea. It can occur with gastric and duodenal ulceration and gastric cancer, but most commonly it is of uncertain origin.

Patients with non-ulcer dyspepsia should be advised to avoid smoking, alcohol, and aggravating foods, and to eat small regular meals to aid digestion. Non-ulcer dyspepsia tends to be self-limiting but antacids and H₂-receptor antagonists are often used to suppress gastric acid; *H. pylori* eradication does not improve symptoms in cases of non-ulcer dyspepsia.

Prompt investigation is important in the presence of severe symptoms such as bleeding, dysphagia, or weight loss.

Gastro-esophageal reflux disease

Gastro-esophageal reflux disease (including non-erosive gastro-esophageal reflux and erosive esophagitis) is associated with a range of symptoms, which include heartburn, acid regurgitation, and sometimes difficulty in swallowing (dysphagia); esophageal inflammation (esophagitis), ulceration, and stricture formation may occur and there is an association with asthma.

The management of gastro-esophageal reflux disease includes drug treatment, lifestyle changes and, in some cases, surgery. Initial treatment is guided by the severity of symptoms; treatment is then adjusted according to response.

For mild symptoms of gastro-esophageal reflux disease, initial management may include the use of antacids. H₂-receptor antagonists suppress acid secretion and they may relieve symptoms and permit reduction in antacid consumption. For refractory cases, and in patients with severe symptoms or proven or severe pathology (for example, Barrett's esophagus), a short course of a proton-pump inhibitor is needed initially.

Zollinger-Ellison syndrome

Management of Zollinger-Ellison syndrome requires high-dose H₂-receptor antagonist treatment. Although proton-pump inhibitors are more effective than the H₂-receptor antagonists, particularly for cases resistant to other treatments, they are more expensive.

- **Aluminium hydroxide**

- **Dosage form**

- Tablets: 300 mg and 500 mg
 - Oral liquid: 320 mg/5 ml in 200 ml bottle

- **Uses**

- Ulcer and non-ulcer dyspepsia
 - Gastro-esophageal reflux disease
 - Hyperphosphatemia

- **Contraindications**

- Hypophosphatemia
 - Undiagnosed gastrointestinal or rectal bleeding
 - Appendicitis
 - Porphyria

- **Precautions**

- Impaired renal function and renal dialysis: Appendix D
 - Hepatic impairment: Appendix E
 - Constipation
 - Dehydration
 - Fluid restriction
 - Gastrointestinal disorders associated with decreased bowel motility or obstruction
 - **Interactions:** Appendix A

- **Dose**

Dyspepsia, gastro-esophageal reflux disease, by mouth

- **ADULT:** 1–2 tablets chewed 4 times daily between meals *plus* at bedtime or 5–10 ml suspension 4 times daily, between meals *plus* at bedtime

- **CHILD** 6–12 years: 5 ml up to 3 times daily

Hyperphosphatemia, by mouth

- **ADULT:** 2–10 g daily in divided doses with meals

Patient advice: Do not take other medicines within 2–4 hours of aluminium hydroxide preparations. May be taken with water to reduce constipating effects.

- **Adverse effects**

- Constipation
- Intestinal obstruction (with large doses)
- Hypophosphatemia with increased bone resorption, hypercalciuria, and increased risk of osteomalacia (more common in patients on a low-phosphate diet or on prolonged therapy)
- Hyperaluminemia resulting in osteomalacia, encephalopathy, dementia, and microcytic anemia (in chronic renal failure treated with aluminium hydroxide as phosphate-binding agent)

- **Magnesium hydroxide**

- **Dosage form**

- Oral liquid: 8% in 200 ml bottle; also in combination with aluminium hydroxide, simethicone, oxetacain

- **Uses**

- Ulcer and non-ulcer dyspepsia
- Gastro-esophageal reflux disease

- **Contraindications**

- Severe renal impairment

- **Precautions**

- Renal impairment: Appendix D
- Hepatic impairment: Appendix E
- **Interactions:** Appendix A

- **Dose**

Dyspepsia, gastro-esophageal reflux disease, by mouth

- **ADULT:** 5–10 ml repeated according to patient's needs

- **Adverse effects**

- Diarrhea
- Hypermagnesemia resulting in loss of deep-tendon reflexes and respiratory depression, along with other symptoms including nausea, vomiting, flushing of skin, thirst, hypotension, drowsiness, confusion, muscle weakness, bradycardia, coma, and cardiac arrest (in renal impairment)

- **Magnesium trisilicate**

These tablets, called antacids, are commonly used in various treatments of indigestion. Antacids are used to reduce the acidity of the gastric juice. Excessive gastric acidity can cause symptoms such as heartburn and indigestion and may injure the gastric wall and cause inflammation of the lining of the stomach or peptic ulcer. Antacids neutralize stomach acid and help relieve the symptoms of heartburn and indigestion.

- **Dosage form**

- Tablets: 250 mg and 500 mg, aluminium hydroxide 120 mg + magnesium trisilicate 250 mg, aluminium hydroxide 250 mg + 500 mg magnesium trisilicate

- **Uses**

- Pain, indigestion, and heartburn; relieving stomach discomfort associated with stomach pain and burning, nausea and excess gas (dyspepsia)

- **Dose**

- **ADULT** and **CHILD** over 12 years: 1 or 2 tablets (chewable) by mouth when needed to relieve the symptoms of heartburn. Sometimes indigestion and heartburn can be the symptoms of more serious conditions such as stomach ulcer or stomach cancer. For this reason, doctor should be consulted before taking this medicine.

Patient advice: There should be at least 2 hours' gap between taking antacids and other medicines.

- **Adverse effects**

- Stomach pain, diarrhea, bloating and gas
- Long-term use can cause kidney stones.
- Antacids can reduce the absorption of many drugs.

- **Omeprazole**

- **Dosage form**

- Capsules: 20 mg and 40 mg
- Injection: 40 mg/vial (sodium)

- **Uses**

- Benign gastric and duodenal ulcers
- Zollinger–Ellison syndrome, before surgery
- Gastro-esophageal reflux disease
- Gastric acid reduction during general anesthesia
- NSAID-associated duodenal or gastric ulcers

- **Precautions**

- Proton-pump inhibitors may mask the symptoms of gastric cancer.
- Particular care is required in those presenting with “alarm features.” In such cases, gastric malignancy should be ruled out before treatment.
- Patients at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D, and, if necessary, receive other preventive therapy.
- Measurement of serum-magnesium concentrations should be considered before and during prolonged treatment with other drugs that cause hypomagnesemia or with digoxin.
- A proton-pump inhibitor should be prescribed for appropriate indications at the lowest effective dose for the shortest period; the need for long-term treatment should be reviewed periodically.
- **Interactions:** Appendix A (Proton-pump inhibitors)

- **Dose**

Benign gastric and duodenal ulcers, by mouth

- **ADULT:** 20 mg once daily for 4 weeks in duodenal ulceration or 8 weeks in gastric ulceration
- In severe or recurrent cases increase to 40 mg daily
- Maintenance for recurrent duodenal ulcer, 20 mg once daily
- Prevention of relapse in duodenal ulcer, 10 mg daily increasing to 20 mg once daily if symptoms return
- NSAID-associated duodenal or gastric ulcer and gastro-duodenal erosions, 20 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed
- Prophylaxis in patients with a history of NSAID-associated duodenal or gastric ulcers, gastro-duodenal lesions, or dyspeptic symptoms who require continued NSAID treatment, 20 mg once daily

- Duodenal or benign gastric ulcer associated with *H. pylori*; *see* Eradication regimens in the introductory notes under Peptic ulcer

Zollinger–Ellison syndrome, by mouth

- Initially 60 mg once daily; usual range 20–120 mg daily (above 80 mg in 2 divided doses)

Gastric acid reduction during general anesthesia (prophylaxis of acid aspiration), by mouth

- 40 mg on the preceding evening then 40 mg 2–6 hours before surgery

Gastro-esophageal reflux disease, by mouth

- 20 mg once daily for 4 weeks, continued for further 4–8 weeks if not fully healed
- 40 mg once daily has been given for 8 weeks in gastro-esophageal reflux disease refractory to other treatment.
- Maintenance 20 mg once daily

Acid reflux disease (long-term management), by mouth

- 10 mg daily increasing to 20 mg once daily if symptoms return

Acid-related dyspepsia, by mouth

- 10–20 mg once daily for 2–4 weeks according to response

Severe ulcerating reflux esophagitis, by mouth

- **CHILD** over 1 year, body weight 10–20 kg: 10 mg once daily increased if necessary to 20 mg once daily for 4–12 weeks
- **CHILD** over 1 year, body weight over 20 kg: 20 mg once daily increased if necessary to 40 mg once daily for 4–12 weeks; to be initiated by hospital pediatrician

By intravenous injection over 5 minutes or by intravenous infusion over 20–30 minutes, prophylaxis of acid aspiration

- 40 mg completed 1 hour before surgery

By intravenous injection over 5 minutes or by intravenous infusion over 20–30 minutes, benign gastric ulcer, duodenal ulcer and gastro-esophageal reflux disease

- 40 mg once daily until oral administration possible

Major peptic ulcer bleeding (following endoscopic treatment)

[unlicensed indication]

- Initial *intravenous infusion* of 80 mg over 40–60 minutes, then by *continuous intravenous infusion*, 8 mg/hour for 72 hours (then change to oral therapy)

○ **Adverse effects**

Of the proton-pump inhibitors

- Gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, flatulence, diarrhea, constipation), headache
- Less frequently dry mouth, peripheral edema, dizziness, sleep disturbances, fatigue, paresthesia, arthralgia, myalgia, rash, and pruritus
- Rarely or very rarely taste disturbance, stomatitis, hepatitis, jaundice, hypersensitivity reactions (including anaphylaxis, bronchospasm), fever, depression, hallucinations, confusion, gynecomastia, interstitial nephritis, hyponatremia, blood disorders (including leukopenia, leukocytosis, pancytopenia, thrombocytopenia), visual disturbances, sweating, photosensitivity, alopecia, Stevens-Johnson syndrome, and toxic epidermal necrolysis
- By decreasing gastric acidity, proton-pump inhibitors may increase the risk of gastrointestinal infections (including *Clostridium difficile* infection)
- Also agitation and impotence

- **Ranitidine**

Ranitidine is a representative H₂-receptor antagonist. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 150 mg and 300 mg (hydrochloride)
- Injection: 25 mg/ml in 2 ml ampoule

- **Uses**

- Benign gastric and duodenal ulceration, gastro-esophageal reflux disease, Zollinger-Ellison syndrome
- Other conditions where gastric acid reduction is beneficial

- **Contraindication**

- Porphyria

- **Precautions**

- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Middle-aged or older patients and those whose symptoms change (may mask symptoms of gastric cancer)
- **Interactions:** Appendix A

- **Dose**

Benign gastric and duodenal ulceration, by mouth

- **ADULT:** 150 mg twice daily or 300 mg at night for 4–8 weeks (up to 6 weeks in chronic episodic dyspepsia and up to 8 weeks in NSAID-

associated ulceration; in NSAID-associated duodenal ulceration, 300 mg can be given twice daily for 4 weeks to achieve a higher healing rate)

- **CHILD** (peptic ulcer): 2–4 mg/kg twice daily (max. 300 mg daily)

Benign gastric and duodenal ulceration, reflux esophagitis, Zollinger-Ellison syndrome, by intramuscular injection

- **ADULT:** 50 mg every 6–8 hours

Benign gastric and duodenal ulceration, reflux esophagitis, Zollinger-Ellison syndrome, by slow intravenous injection

- **ADULT:** 50 mg diluted to 20 ml and given over at least 2 minutes (may be repeated every 6–8 hours)

Benign gastric and duodenal ulceration, reflux esophagitis, Zollinger-Ellison syndrome, by intravenous infusion

- **ADULT:** 25 mg/hour for 2 hours (may be repeated every 6–8 hours)

Duodenal ulceration associated with H. pylori

- See note above.

Prophylaxis of NSAID-induced gastric or duodenal ulcer, by mouth

- **ADULT:** 300 mg twice daily

Gastro-esophageal reflux disease, by mouth

- **ADULT:** 150 mg twice daily or 300 mg at night for up to 8 weeks, or if necessary, 12 weeks, increased in moderate-to-severe disease to 600 mg daily in 2–4 divided doses for up to 12 weeks

Long-term treatment of healed gastro-esophageal reflux disease, by mouth

- **ADULT:** 150 mg twice daily

Zollinger-Ellison syndrome, by mouth

- **ADULT:** 150 mg 3 times daily; up to 6 g daily in divided doses has been used

Gastric acid reduction (prophylaxis of acid aspiration) in obstetrics, by mouth

- **ADULT:** 150 mg at onset of labor, then every 6 hours

Surgical procedures, by intramuscular or slow intravenous injection

- **ADULT:** 50 mg 45–60 minutes before induction of anesthesia (intravenous injection diluted to 20 ml and given over at least 2 minutes)

Surgical procedures, by mouth

- **ADULT:** 150 mg 2 hours before induction of anesthesia, and also, when possible, on the preceding evening

Prophylaxis of stress ulceration, by slow intravenous injection

- **ADULT:** Initially 50 mg diluted to 20 ml and given over at least 2 minutes, then 125–250 micrograms/kg per hour *by continuous intravenous infusion* (may be followed by 150 mg twice daily *by mouth* when oral feeding commences)

○ **Adverse effects**

- Diarrhea and other gastrointestinal disturbances, headache, dizziness, rash, tiredness, acute pancreatitis, bradycardia, atrioventricular block, confusion, depression
- Rarely hallucinations (particularly in the elderly or very ill), hypersensitivity reactions (including fever, arthralgia, myalgia, and anaphylaxis), blood disorders (including agranulocytosis, leukopenia, pancytopenia, and thrombocytopenia), hepatitis, tachycardia, agitation,

visual disturbances, erythema multiforme, alopecia, gynecomastia, and impotence

- Very rarely interstitial nephritis

17.2 ANTI-EMETIC MEDICINES

Metoclopramide has anti-emetic properties and also stimulates upper gastrointestinal motility. Metoclopramide is effective against nausea and vomiting associated with gastrointestinal disorders or migraine, and following surgery and chemotherapy; it is also effective against radiation-induced nausea and vomiting. Combining metoclopramide with corticosteroids (such as dexamethasone) can improve its anti-emetic effect in chemotherapy-induced nausea and vomiting (*see also* Section 8.2). Metoclopramide may be useful in the management of gastro-esophageal reflux disease (Section 17.1) and gastroparesis, as well as preoperatively in the prevention of aspiration syndromes. It is also used to facilitate intubation of the small bowel during radiographic examinations. Metoclopramide is **not** effective in the prevention or treatment of motion sickness.

Metoclopramide may cause acute dystonic reactions with facial and skeletal muscle spasms and oculogyric crises. These reactions are most common in the young (especially girls and young women) and the elderly; they occur shortly after the start of treatment and subside within 24 hours of drug withdrawal.

Promethazine is a phenothiazine that, in addition to D2 dopaminergic blockade, has pronounced histamine H1 and muscarinic-receptor-blocking properties. It is effective in the prevention and treatment of vertigo and motion sickness. Promethazine may be useful in the prevention and treatment of postoperative and drug-induced nausea and vomiting. It has limited effect on chemotherapy-induced mild-to-moderate emesis.

- **Chlorpromazine**

- **Dosage form**

- Tablets: 25 mg, 50 mg, and 100 mg (as hydrochloride)

- Injection: 25 mg/ml in 2 ml ampoule (as hydrochloride)
- **Uses**
 - Severe vomiting where other drugs have failed or are not available
 - Schizophrenia and other psychotic disorders, mania, psychomotor agitation, and violent behavior
 - Adjunct in severe anxiety (Section 24.1)
- **Contraindications**
 - See Section 24.1.
- **Precautions**
 - See Section 24.1.
 - **Skilled tasks:** May impair ability to perform skilled tasks (or example, operating machinery or driving)
- **Dose**

By mouth

- **ADULT:** 10–25 mg every 4–6 hours
- **CHILD:** 500 micrograms/kg every 4–6 hours (**CHILD** 1–5 years: maximum 40 mg daily; **CHILD** 6–12 years: max. 75 mg daily)

By deep intramuscular injection

- **ADULT:** Initially 25 mg, then 25–50 mg every 3–4 hours until vomiting stops
- **CHILD:** 500 micrograms/kg every 6–8 hours (**CHILD** 1–5 years: maximum 40 mg daily; **CHILD** 6–12 years: max. 75 mg daily)

- **Adverse effects**
 - See Section 24.1.

- **Dimenhydrinate**

- **Dosage form**

- Tablet: 50 mg
 - Injection: 50 mg/ml in 1 ml injectable ampoule
 - Oral syrup: 3.125 mg/ml in 60 ml bottle

- **Uses**

- Treatment and prevention of travelers' diseases and symptomatic treatment of nausea and confusion in Menière disease and other atrial disorders

- **Contraindication**

- Not safe in porphyria patients

- **Precautions**

- Administer with caution in patients with liver diseases and epilepsy, in children and the elderly, and in pregnancy.

Patient advice: Avoid working in high altitudes; avoid operating machines and driving.

- **Precautions**

- **Interactions:** As with other sedative antihistamines

- **Dose**

Orally

- **ADULT:** 50–100 mg, 3–4 times daily. To prevent travel sickness, the first dose should be given 30 minutes before the start of the trip.

Intramuscular injection

- **ADULT:** 50 mg with 5% concentration and 0.5% intravenous injection slowly (administered in 2 minutes).

Symptomatic treatment of nausea and confusion in children

- **CHILD** 2–6 years: 12.5–25 mg administered 3-4 times daily (max. dose 75 mg)
- **CHILD** 6–12 years old: 25–50 mg administered 3-4 times daily (max. dose is 150 mg)

Intramuscular injection in children

- **CHILD:** 12.5 mg per kg body weight administered up to 4 times daily (max. 300 mg daily)

○ **Adverse effects**

- As with other sedative antihistamines, the most common side effects are mild-to-profound drowsiness, lethargy, confusion, and ataxia (although with high doses or in children and older individuals may inversely cause nerve stimulation), but these side effects may decrease after a few days of continuous treatment.
- Other common side effects include headache, motion-nervous disorders and antimuscarinic effects (for example, urine retention, dry mouth, and sight and gastrointestinal disorders), cardiac palpitations and arrhythmia, hypertension, hypersensitivity reactions (including bronchial constriction, angioedema, and anaphylaxis), cutaneous lesions and allergic reactions, extrapyramidal symptoms, impaired consciousness, mental depression, sleep disorders, tremors, convulsions, sweating, muscle pain, numbness, blood disorders, liver disorders, and hair loss.

- **Diphenhydramine teoclate (diphenhydramine + theophylline)**
 - **Dosage form**
 - Tablet: 50 mg
 - Injection: 50 mg/ml injectable vial
 - **Uses**
 - Treatment and prevention of travelers' diseases
 - Symptomatic treatment of nausea and light-headedness due to Menière's disease and other vestibular disorders
 - **Precautions**
 - Porphyria
 - Pregnancy: Appendix B
 - **Interactions:** Appendix A
 - **Dose**
 - **ADULT:** 50–100 mg 3–4 times daily. The first dose for the prevention of travelers' diseases should be taken at least 30 minutes before traveling.
 - **CHILD** 2–6 years old: 12–25 mg every 6–8 hours (max. dose 75 mg)
 - **CHILD** 6–12 years old: 25–50 mg every 6–8 hours (max. dose 150 mg)
- Intramuscular injection*
- **ADULT:** 50 mg (or by *slow intravenous injection*)
 - **CHILD:** 1.25 mg/kg body weight up to 4 times daily, administered intramuscularly in children; maximum 300 mg per day prescribed
- **Adverse effects**
 - Identification disorders or differentiation of color, night vision (ability to see in low light due to a side effect on photoreceptor proteins in the photoreceptor cells of the eye)

- **Metoclopramide**

- **Dosage form**

- Tablet: 10 mg (hydrochloride)
 - Injection: 5 mg (hydrochloride)/ml in 2 ml ampoule
 - *Oral drops: 4 mg/ml**
 - *Oral syrup: 5 mg/5 ml**

- **Uses**

- Nausea and vomiting in gastrointestinal disorders, in migraine, and following surgery and treatment with cytotoxics or radiotherapy
 - Gastro-esophageal reflux disease
 - Premedication
 - Aid to gastrointestinal intubation
 - Gastroparesis

Note: In children (and in some countries, patients under 20 years) use is restricted to treatment of severe intractable vomiting of known cause, management of radio- and chemotherapy-induced nausea and vomiting, as an aid to gastrointestinal intubation, and as premedication.

- **Contraindications**

- Gastrointestinal obstruction, hemorrhage, or perforation
 - 3–4 days after gastrointestinal surgery
 - Convulsive disorders
 - Pheochromocytoma

- **Precautions**

- Elderly, children, and young adults
 - Hepatic impairment: Appendix E
 - Renal impairment: Appendix D

- May mask underlying disorders such as cerebral irritation
- Avoid for 3–4 days after gastrointestinal surgery.
- Pregnancy: Appendix B
- Breast-feeding: Appendix V
- Parkinson's disease
- Epilepsy
- Depression
- Porphyria
- **Interactions:** Appendix A

○ **Dose**

Nausea and vomiting, gastro-esophageal reflux disease, gastroparesis, by mouth, by intramuscular injection, or by slow intravenous injection (over 1–2 minutes)

- **ADULT:** 10 mg 3 times daily
- **YOUNG ADULT** 15–19 years (under 60 kg): 5 mg 3 times daily
- **CHILD** up to 1 year (up to 10 kg): 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 3 times daily
- **CHILD** 9–14 years (30 kg and over): 5 mg 3 times daily
- Usual maximum dose is 500 micrograms/kg daily, particularly for children and young adults.

Premedication, by slow intravenous injection

- **ADULT:** 10 mg as a single dose

Aid to gastrointestinal intubation, by mouth, by intramuscular injection, or by slow intravenous injection

- **ADULT:** 10–20 g as a single dose 5–10 minutes before examination
- **YOUNG ADULT** (15–19 years): 10 mg
- **CHILD** under 3 years: 1 mg
- **CHILD** 3–5 years: 2 mg
- **CHILD** 5–9 years: 2.5 mg
- **CHILD** 9–14 years: 5 mg

Note: High-dose metoclopramide with cytotoxic chemotherapy, *see* Section 8.2.

- **Adverse effects**

- Extrapyramidal symptoms (especially in children and young adults)
- Tardive dyskinesias on prolonged use
- Hyperprolactinemia
- Drowsiness, restlessness, dizziness, headache, diarrhea, depression, hypotension, and hypertension reported
- Rarely neuroleptic malignant syndrome
- Rash, pruritus, edema
- Cardiac conduction abnormalities following intravenous administration
- Rarely methemoglobinemia (more severe in G6PD deficiency)

- **Promethazine**

- **Dosage form**

- Tablet: 25 mg (hydrochloride)
- Injection: 25 mg (hydrochloride)/ml in 2 ml ampoule
- Oral syrup: 5 mg (hydrochloride)/5 ml

- **Uses**

- Management of postoperative and drug-induced nausea and vomiting
- Labyrinthine disorders, motion sickness
- Premedication (Section 1.3)

- Treatment of allergy (Section 3)
- **Contraindications**
 - Porphyria
 - Child under 2 years (risk of respiratory depression)
- **Precautions**
 - Prostatic hypertrophy
 - Urinary retention
 - Glaucoma
 - Pyloroduodenal obstruction
 - Hepatic disease: Appendix E
 - Epilepsy
 - Elderly and children (more susceptible to adverse effects)
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A
 - **Skilled tasks:** May impair ability to perform skilled tasks (for example operating machinery or driving)
- **Dose**

Nausea and vomiting, by mouth

- **ADULT:** 25 mg at night, increased to 50–75 mg at night or 25 mg 2–3 times daily if necessary (max. 100 mg in 24 hours)

*By deep intramuscular injection or by slow intravenous injection
(diluted to 2.5 mg/mL in water for injection)*

- **ADULT:** 12.5–25 mg, repeated at intervals of not less than 4 hours (usual max. 100 mg in 24 hours)

Prevention of motion sickness, by mouth

- **ADULT:** 20–25 mg at bedtime on night before travel, repeated on the morning of travel if necessary
- **CHILD** 2–5 years: 5 mg at bedtime on night before travel and also on morning of travel if necessary
- **CHILD** 5–10 years: 10 mg at bedtime on night before travel and also on morning of travel if necessary

Dilution and administration: According to manufacturer's directions

○ **Adverse effects**

- Drowsiness, dizziness, sedation (paradoxical stimulation may occur, especially with high doses or in children and the elderly)
- Headache, nightmares, confusion, psychomotor impairment
- Urinary retention, dry mouth, blurred vision, gastrointestinal disturbances
- Extrapyrarnidal effects
- Hypersensitivity reactions
- Rash, photosensitivity reactions
- Jaundice
- Blood disorders
- Cardiovascular adverse effects (after injection)
- Venous thrombosis at site of intravenous injection
- Pain on intramuscular injection

17.3 ANTI-INFLAMMATORY MEDICINES

Ulcerative colitis and Crohn's disease are chronic inflammatory diseases of the intestinal tract. Effective management requires drug therapy, attention to nutrition, and in severe or chronic active disease, surgery.

Acute attacks of mild-to-moderate severity affecting the rectum (proctitis) or the rectosigmoid (distal colitis) require local treatment with a corticosteroid (such as **hydrocortisone**) or an aminosalicylate (such as **sulfasalazine**). More extensive disease, or disease that is not responsive to local treatment, requires oral therapy; an oral aminosalicylate alone can sometimes be used in mild disease affecting the colon but addition of an oral corticosteroid for 4–8 weeks is usually necessary. Because of the risk of intestinal perforation, rectal forms of hydrocortisone must be used with extreme caution in patients with severe ulcerative disease and should not be given to such patients without conducting a thorough proctological examination.

Severe extensive or fulminant disease needs hospital admission and intravenous corticosteroid administration; other therapy may include intravenous fluid and electrolyte replacement, blood transfusion, and possibly parenteral nutrition and antibacterials.

Metronidazole (Section 6.2.2) may be beneficial in the treatment of active Crohn's disease, particularly with perianal involvement, possibly through its antibacterial activity. Other antibacterials should be given if specifically indicated (for example, in sepsis associated with fistulas and perianal disease) and for managing bacterial overgrowth in the small bowel.

Immunosuppressant drugs can be useful in patients with chronically active disease, particularly in patients unresponsive to corticosteroids or those with corticosteroid-dependent disease. Methotrexate (Section 2.4) is sometimes used to treat Crohn's disease unresponsive to other immunosuppressants.

Sulfasalazine is most effective in the *maintenance of remission* of ulcerative colitis, but it is not so useful in Crohn's disease. Corticosteroids are not suitable for maintenance of remission because of their adverse effects. In resistant or frequently relapsing cases of inflammatory bowel disease, azathioprine, 2–2.5 mg/kg daily (Section 8.1), or mercaptopurine, 1–1.5 mg/kg daily (Section 8.2) given under close supervision may be

helpful. Methotrexate, 15 mg weekly, is sometimes used to maintain remission in Crohn's disease.

Additional treatments: Laxatives are required to facilitate bowel movement when proctitis is present. Antimotility drugs such as codeine and antispasmodic drugs should **not** be used in active ulcerative colitis because they can precipitate paralytic ileus and megacolon. Diarrhea resulting from reduced bile salt absorption may improve with colestyramine. General nutritional care and appropriate supplements are essential. High-fiber or low-residue diets should be used as appropriate. Irritable bowel syndrome during remission of ulcerative colitis requires avoidance of a high-fiber diet and possibly treatment with an antispasmodic.

- **Sulfasalazine**

Sulfasalazine is a representative aminosalicylate. Various medicines can serve as alternatives.

- **Dosage form**

- Tablet: 500 mg

- **Uses**

- Ulcerative colitis
 - Crohn's disease
 - Severe rheumatoid arthritis (Section 2.4)

- **Contraindications**

- Hypersensitivity to salicylates or sulfonamides
 - Children under 2 years
 - Porphyria
 - Intestinal or urinary obstruction
 - Severe renal impairment

- **Precautions**

- See Section 2.4.
- **Interactions:** Appendix A
- **Blood disorders:** Patients should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever, or malaise occurring during treatment; blood count should be performed and sulfasalazine stopped immediately if there is suspicion or evidence of blood disorder.

- **Dose**

Ulcerative colitis, by mouth

- **ADULT:** 1–2 g 4 times daily in acute attack until remission, reducing to a maintenance dose of 500 mg 4 times daily
- **CHILD** over 2 years: 40–60 mg/kg daily in acute attack, reducing to a maintenance dose of 20–30 mg/kg daily

Active Crohn's disease, by mouth

- **ADULT:** 1–2 g 4 times daily in acute attack until remission occurs
- **CHILD** over 2 years: 40–60 mg/kg daily in acute attack until remission occurs

- **Adverse effects**

- See Section 2.4.

17.4 LAXATIVES

A balanced diet, including adequate fluid intake and fiber, is of value in preventing constipation.

Before prescribing laxatives, it is important to be sure that the patient is constipated and that the constipation is not secondary to an underlying undiagnosed complaint. It is also important that the patient understands that bowel habit can vary considerably in

frequency without doing harm. For example, some people consider themselves constipated if they do not have a bowel movement each day. A useful definition of constipation is the passage of hard stools less frequently than the patient's own normal pattern; this should be explained to the patient since misconceptions about bowel habits have led to excessive laxative use, which in turn has led to hypokalemia.

Laxatives should generally be avoided except where straining will exacerbate a condition such as angina or increase the risk of rectal bleeding, as in hemorrhoids. Laxatives are of value in drug-induced constipation, for the expulsion of parasites after anthelmintic treatment (Section 6.1) and to clear the alimentary tract before surgery and radiological procedures. Prolonged treatment of constipation is sometimes necessary.

There are many different laxatives. These include bulk-forming laxatives, which relieve constipation by increasing fecal mass and stimulating peristalsis; stimulant laxatives (such as senna), which increase intestinal motility and often cause abdominal cramp; fecal softeners, which lubricate and soften impacted feces; and osmotic laxatives, which act by retaining fluid in the bowel by osmosis. Bowel-cleansing solutions are used before colonic surgery, colonoscopy, or radiological examination to ensure that the bowel is free of solid contents; they are not a treatment for constipation.

- **Bisacodyl**

- **Dosage form**

- Tablet: 5 mg

- **Uses**

- For relief of constipation before diagnostic procedures and colon surgery

- **Contraindications**

- Intestinal obstruction
 - Severe dehydration
 - Acute surgical abdominal conditions

- Acute inflammatory bowel disease
- **Precautions**
 - Avoid excessive use unless prevention of stool hardening is needed.
 - Pregnancy: Appendix B
- **Dose**

Constipation, by mouth

- **ADULT:** 5–10 mg at night, increased if necessary to maximum 20 mg at night
- **CHILD** 4–18 years: 5–20 mg once daily, adjusted according to response
- **CHILD** 2–18 years: 5–10 mg once daily, adjusted according to response

Before radiological procedures and surgery, by mouth

- 10 mg in the morning and 10 mg in the evening on the day before procedure

Note: Tablets act in 10–12 hours.

- **Adverse effects**
 - Excessive use of stimulant laxatives can cause diarrhea and related effects such as hypokalemia
 - Nausea and vomiting
 - Colitis also reported
- **Lactulose**
 - **Dosage form**
 - Oral syrup: 3.33 g/5 ml in 150 ml bottle
 - **Uses**

- Constipation (may take up to 48 hours to act)
- Hepatic encephalopathy (portal systemic encephalopathy)
- **Contraindications**
 - Galactosemia
 - Intestinal obstruction
- **Precautions**
 - Lactose intolerance
 - In pregnancy, not known to be harmful
 - **Interactions:** Appendix A
- **Dose**

Constipation, by mouth

- **ADULT:** Initially 15 ml twice daily, adjusted according to response
- **CHILD** under 1 year: 2.5 ml twice daily, adjusted according to response
- **CHILD** 1–5 years: 2.5–10 ml twice daily, adjusted according to response
- **CHILD** 5–18 years: 5–20 ml twice daily, adjusted according to response

Hepatic encephalopathy, by mouth

- **ADULT:** 30–50 ml 3 times daily, subsequently adjusted to produce 2–3 soft stools daily
- **CHILD** 12–18 years: 30–50 ml 3 times daily; adjust dose to produce 2–3 soft stools per day

- **Adverse effects**
 - Nausea (can be reduced by administration with water or fruit juice, or with meals)
 - Vomiting
 - Flatulence

- Cramps and abdominal discomfort

17.5 MEDICINES USED IN DIARRHEA

Acute diarrheal diseases are a leading cause of childhood morbidity and mortality; frail and elderly patients are also at risk. In adults, acute diarrhea is the most frequent health problem of travelers to developing countries and is increasingly common among HIV-infected persons. Assessment and correction of dehydration and electrolyte disturbance is the priority in all cases of acute diarrhea. Symptomatic relief (Section 17.5.3) in adults may be warranted in some cases but antidiarrheals should never be used in children since they do not reduce fluid and electrolyte loss and may cause adverse effects.

Diarrhea persisting for longer than a month is known as chronic diarrhea. A mild malabsorption syndrome, tropical enteropathy, is apparent in most healthy indigenous populations of tropical countries. However, the majority of cases of chronic diarrhea have non-infectious causes such as gluten sensitivity, inherited metabolic disorders, or inflammatory bowel disease. Bloody diarrhea is usually a sign of invasive enteric infection and should be treated with an appropriate anti-infective agent (Section 6).

17.5.1 Oral rehydration

Replacement of fluid and electrolytes orally can be achieved by giving *oral rehydration salts* (solutions containing sodium, potassium, citrate and glucose). Acute diarrhea in children should always be treated with oral rehydration solution, according to plans A, B, or C as detailed below.

Treatment of dehydration in children: WHO recommendations

According to the degree of dehydration in diarrhea, health professionals are advised to follow one of three management plans.

Plan A

No dehydration. Nutritional advice, increased fluid intake (in the form of soup, rice, water, yoghurt, or even just water), and zinc supplementation (Section 17.5.2) at home are usually sufficient. However, for infants aged under 6 months who have not yet started taking solids, oral rehydration solution must be presented before offering milk. Mother's milk or dried cow's milk must be given without any particular restrictions. In the case of mixed breast-milk/formula feeding, the contribution of breast-feeding should be increased.

Plan B

Moderate dehydration. Whatever the child's age, a 4-hour treatment plan is used to avoid short-term problems. It is recommended that parents are shown how to give approximately 75 ml/kg of oral rehydration solution (in small amounts and at regular intervals) over a 4-hour period. It is suggested that parents should be observed to see how they cope at the beginning of the treatment. A larger amount of solution can be given if the child continues to have frequent stools. In the event of vomiting, rehydration must be discontinued for 10 minutes and then resumed at a slower rate. In young children, breast-feeding should be continued on demand; 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. Zinc supplementation (Section 17.5.2) should begin as soon as the child can eat and has completed 4 hours of oral rehydration. Oral rehydration solution should continue to be offered once dehydration has been controlled, for as long as the child continues to have diarrhea.

Plan C

Severe dehydration. Hospitalization is necessary, but the most urgent priority is to start rehydration. In the hospital (or elsewhere), if the child can drink, oral rehydration solution must be given pending, and even during, intravenous infusion (20 ml/kg every

hour by mouth before infusion, then 5 ml/kg every hour by mouth during intravenous rehydration). For intravenous supplementation, it is recommended that a compound solution of sodium lactate (or, if this is unavailable, sodium chloride, 0.9% solution) is administered at a rate adapted to the child's age (infant under 12 months; 30 ml/kg over 1 hour then 70 ml/kg over 5 hours; child over 12 months; 30 ml/kg over 30 minutes then 70 ml/kg over 2.5 hours). If the intravenous route is unavailable, a nasogastric tube is also suitable for administering oral rehydration solution at a rate of 20 ml/kg every hour for 6 hours. 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.

- **Oral rehydration salts**

- **Composition**

- Glucose: 75 mEq
 - Sodium: 75 mEq or mmol/L
 - Chloride: 65 mEq or mmol/L
 - Potassium: 20mEq or mmol/L
 - Citrate: 10 mmol/L; osmolarity: 245 mOsm/L
 - Glucose: 13.5 g/L
 - Sodium chloride: 2.6 g/L
 - Potassium chloride: 1.5 g/L
 - Trisodium citrate dihydrate+: 2.9 g/L
 - Trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.

Glucose salt solution

Sodium chloride	2.6 g/L of clean water
Sodium citrate (dihydrate)	2.9 g/L of clean water

Potassium chloride	1.5 g/L of clean water
Glucose (anhydrous)	13.5 g/L of clean water

When glucose and sodium citrate are not available, replace with the following

Sucrose (common sugar)	27 g/L of clean water
Sodium bicarbonate	2.5 g/L of clean water

Note: The solution may be prepared either from prepackaged sugar/salt mixtures or from bulk substances and water. Solutions must be freshly prepared, preferably with recently boiled and cooled water. Accurate weighing and thorough mixing and dissolution of ingredients in the correct volume of clean water are important. Administration of more concentrated solutions can result in hypernatremia.

- **Uses**
 - Dehydration from acute diarrhea
- **Precaution**
 - Renal impairment: Appendix D
- **Dose**

Fluid and electrolyte loss in acute diarrhea, by mouth

- **ADULT:** 200–400 ml solution after every loose motion
- **INFANT** and **CHILD:** According to Plans A, B, or C (see introductory notes)

- **Adverse effects**

- Vomiting (may indicate too rapid administration)
- Hyponatremia and hyperkalemia (may result from overdose in renal impairment or administration of too concentrated a solution)

17.5.2 Medicines for diarrhea in children

- **Zinc sulfate**

Zinc supplementation is used in combination with oral rehydration therapy in the management of acute diarrhea in children. Zinc supplements given during an episode of acute diarrhea reduce the severity and duration of the episode; if given for 10–14 days, zinc also reduces the incidence of new episodes of diarrhea in the 2–3 months following treatment.

- **Dosage form**

- Oral liquid: 4 mg per 5 ml
- Tablets: 10 mg and 20 mg per blister pack of 10 tablets

- **Uses**

- Adjunct to oral rehydration therapy in acute diarrhea

- **Precautions**

- Acute renal failure (may accumulate)
- **Interactions:** Appendix A

- **Dose**

Adjunct to oral rehydration therapy in acute diarrhea, by mouth

- **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 sulfate tablets may be dispersed in breast milk, in oral rehydration solution, or in water on a small spoon; older children may chew the tablets or swallow them with water.

- **Adverse effects**
 - Abdominal pain, dyspepsia, nausea, vomiting, diarrhea, gastric irritation, gastritis
 - Irritability, headache, lethargy

17.5.3 Antidiarrheal (symptomatic) medicines in adults

Opioids such as **codeine** are used in the symptomatic relief of uncomplicated, acute diarrhea in adults, but are contraindicated in young children. Codeine acts on opioid receptors in the gut wall and decreases bowel motility. In dehydration, fluid and electrolyte replacement are of primary importance (Section 17.5.1; Section 26).

17.6 MISCELLANEOUS

- **Hyoscine**
 - **Dosage form**
 - Tablet: 10 mg (butylbromide and hydrobromide)
 - Injection: 20 mg/ml (butylbromide and hydrobromide) in 1 ml ampoule
 - **Uses**
 - Symptomatic relief of gastrointestinal or genito-urinary disorders characterized by smooth muscle spasm
 - Bowel colic and excessive respiratory secretions
 - **Contraindications**
 - Myasthenia gravis (but may be used to decrease muscarinic side effects of anticholinesterases)

- Paralytic ileus
 - Pyloric stenosis
 - Toxic megacolon
 - Prostatic enlargement
- **Precautions**
- Down syndrome
 - Children and the elderly
 - They should also be used with caution in gastro-esophageal reflux disease, diarrhea, ulcerative colitis, autonomic neuropathy, acute myocardial infarction, hypertension, conditions characterized by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery), pyrexia, and in individuals susceptible to angle-closure glaucoma.
 - **Interactions:** Appendix A

○ **Dose**

By mouth (but poorly absorbed, see notes above), smooth muscle spasm

- **ADULT:** 20 mg 4 times daily
- **CHILD** 6–12 years: 10 mg 3 times daily

Irritable bowel syndrome

- 10 mg 3 times daily, increased if required up to 20 mg 4 times daily

By intramuscular or slow intravenous injection, acute spasm and spasm in diagnostic procedures

- **ADULT:** 20 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), maximum 100 mg daily
- **CHILD** 2–6 years: 5 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy)

- **CHILD** 6–12 years: 5–10 mg, repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), maximum 30 mg daily
- **CHILD** 12–18 years: 20 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), maximum 80 mg daily

Note: Hyoscine butylbromide tablets can be sold to the public for medically confirmed irritable bowel syndrome, provided single dose does not exceed 20 mg, daily dose does not exceed 80 mg, and pack does not contain a total of more than 240 mg.

○ **Adverse effects**

- Constipation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilation of the pupils with loss of accommodation, photophobia, dry mouth, flushing, and dryness of the skin
- Occasionally confusion (particularly in the elderly), nausea, vomiting, and giddiness
- Very rarely angle-closure glaucoma

SECTION 18: Hormones, other endocrine medicines, and contraceptives

LML strengths and dosage forms are marked in *italic* with an asterisk.

18.1 ADRENAL HORMONES AND SYNTHETIC SUBSTITUTES

Corticosteroids include hormones secreted by the adrenal cortex and synthetic analogues of these hormones. The adrenal cortex normally secretes hydrocortisone, which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone. Synthetic glucocorticoids include **betamethasone**, **dexamethasone**, and **prednisolone**. Although fludrocortisone also has glucocorticoid properties, it is used for its potent mineralocorticoid effects.

In physiological (low) doses, corticosteroids replace deficient endogenous hormones. In pharmacologic (high) doses, glucocorticoids decrease inflammation (see Section 3) and suppress the immune response (see Section 8.1).

In therapeutic doses, glucocorticoids suppress the release of corticotrophin (adrenocorticotrophic hormone, ACTH) from the pituitary gland, and the adrenal cortex ceases secretion of endogenous corticosteroids. If suppressive doses are given for prolonged periods, the adrenal cortex may atrophy; this can lead to a deficiency on sudden withdrawal (or dosage reduction) of the corticosteroid in situations such as stress or trauma, when corticosteroid requirements are increased. After high dosage or prolonged therapy, withdrawal of the corticosteroid should therefore be gradual (see note on Withdrawal of systemic corticosteroids below). The suppressive effect of a corticosteroid on cortisol secretion is least when it is given as a single dose in the morning. Because the therapeutic effects of corticosteroids are of longer duration than the metabolic

effects, intermittent therapy may allow the therapeutic effects to be maintained while reducing the metabolic. Alternate-day dosing is, however, suitable only in certain disease states and for corticosteroids with low mineralocorticoid activity and a relatively short duration of action effects.

Hydrocortisone is used in adrenal replacement therapy and on a short-term basis by intravenous injection for the emergency management of some conditions, for example, anaphylaxis (Section 3). Its mineralocorticoid activity is too high for it to be used on a long-term basis for disease control. The high mineralocorticoid activity of fludrocortisone is used together with a glucocorticoid in adrenal insufficiency.

Prednisolone has predominantly glucocorticoid activity and is usually the preferred corticosteroid for long-term disease control.

Dexamethasone has very high glucocorticoid activity and insignificant mineralocorticoid activity, making it particularly suitable for conditions where water retention would be a disadvantage. It also has a long duration of action and this, together with its lack of mineralocorticoid activity makes it particularly suitable for conditions requiring suppression of corticotrophin secretion, such as congenital adrenal hyperplasia.

Disadvantages of corticosteroids

Overdosage or prolonged use may exaggerate some of the normal physiological actions of corticosteroids leading to mineralocorticoid and glucocorticoid adverse effects.

Mineralocorticoid adverse effects include hypertension, sodium and water retention, and potassium loss. These effects are most marked with fludrocortisones, are significant with hydrocortisone, occur slightly with prednisolone, and are negligible with dexamethasone.

Glucocorticoid adverse effects include diabetes mellitus and osteoporosis; the latter is of particular importance in the elderly since it may result in osteoporotic fractures of the hip or vertebrae. High doses may also be associated with avascular necrosis of the femoral neck. Muscle wasting may also occur and there is a weak link with peptic ulceration. Mental disturbances can occur, including serious paranoid state or depression with risk of suicide, particularly in patients with a history of mental disorders; euphoria is also common. High doses may cause Cushing syndrome, which is characterized by a moon face, striae, and acne; it is usually reversible on withdrawal of treatment, but this should always be tapered gradually to avoid symptoms of acute adrenal insufficiency.

In children, corticosteroids may result in suppression of growth and during pregnancy use of corticosteroids can affect adrenal development in the fetus. Any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important. In all age groups, healing of wounds may be impaired, and infections and thinning of the skin may occur; spread of infections may result from modification of tissue reactions.

Adrenal suppression

Adrenal suppression occurs during prolonged therapy with corticosteroids, leading to the development of adrenal atrophy, which may persist for years after cessation of therapy. Abrupt withdrawal after a prolonged period may therefore result in acute adrenal insufficiency, hypotension or even death (see Withdrawal of Systemic Corticosteroids, below). Withdrawal may also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules, and weight loss.

Corticosteroid cover during stress

To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgery requires a temporary increase in corticosteroid dose, or if recently stopped, a temporary reintroduction of corticosteroid treatment. It is important therefore that anesthetists know whether a patient is taking or has been taking a corticosteroid so as to avoid a precipitous fall in blood pressure during anesthesia or in the immediate postoperative period. Suitable regimens for corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of surgery, are as follows:

- ***Minor surgery under general anesthesia:*** Usual oral corticosteroid dose on the morning of surgery, or hydrocortisone, 25–50 mg, intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery.
- ***Moderate or major surgery:*** Usual oral corticosteroid dose on the morning of surgery and hydrocortisone, 25–50 mg, intravenously at induction of anesthesia, followed by hydrocortisone, 25–50 mg, 3 times a day by intravenous injection for 24 hours after moderate surgery or for 48–72 hours after major surgery; the usual oral corticosteroid dose is recommenced on stopping hydrocortisone injections.

Infections

Prolonged courses of corticosteroids increase susceptibility to infections and increase their severity; clinical presentation of infections may also be atypical. Serious infections—for example, septicemia and tuberculosis—may reach an advanced stage before being recognized; amebiasis and strongyloidiasis may be activated or exacerbated (exclude the possibility of such infections before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral ocular infections may also be exacerbated.

Chicken pox

Unless they have already had chicken pox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at risk of severe chicken pox. Manifestations of fulminant illness include pneumonia, hepatitis, and disseminated intravascular coagulation; rash is not necessarily a prominent feature.

Passive immunization with varicella-zoster immunoglobulin is needed for exposed non-immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months; varicella-zoster immunoglobulin should preferably be given within 3 days of exposure and no later than 10 days following exposure. Confirmed chicken pox warrants specialist care and urgent treatment; in such cases, corticosteroids should not be stopped and the dosage may even need to be increased.

Topical, inhaled, or rectal corticosteroids are less likely to be associated with an increased risk of severe chicken pox.

Measles

Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin (Section 11.2) may be needed.

Dosage and administration

The adverse effects of systemic glucocorticoids, including suppression of the HPA (hypothalamo-pituitary-adrenal) axis, are dose- and duration-dependent; thus patients should be given treatment for the shortest-possible period and at

the lowest dose that is clinically necessary. In life-threatening diseases, high doses are justified because the complications of glucocorticoid therapy are likely to be less serious than the disease itself. In long-term therapy for relatively benign chronic conditions, such as rheumatoid arthritis, the adverse effects often outweigh the advantages. In order to minimize the adverse effects, the maintenance dose should be kept as low as possible and single morning doses or alternate-day therapy should be used in preference to other regimens. Glucocorticoids can improve the prognosis of serious conditions such as systemic lupus erythematosus, temporal arteritis, and polyarteritis nodosa; in such disorders the effects of the disease process may be suppressed and symptoms relieved but the underlying condition is not cured.

A corticosteroid may be used in the management of raised intracranial pressure or cerebral edema that occurs as a result of malignancy; high doses of dexamethasone are generally used for this purpose. However, a corticosteroid should **not** be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.

Glucocorticoids are used both topically and systemically. In emergency situations, hydrocortisone may be given intravenously. Whenever possible, local treatment with creams (for example, in inflammatory skin conditions; see Section 13.3), intra-articular injections, inhalations (for example, in asthma; see Section 25.1), eyedrops (for example, in inflammatory eye conditions; see Section 21.2) or enemas (Section 17.3) should be used in preference to systemic therapy.

Withdrawal of systemic corticosteroids

The rate of withdrawal of systemic glucocorticoids depends upon several factors, including size of dose, duration of treatment, individual response, and likelihood of relapse of the underlying disease. If there is uncertainty about suppression of the HPA axis, withdrawal should be gradual to enable the adrenal gland to

recover. Patients should be advised not to stop taking glucocorticoids abruptly unless instructed to do so by their doctor.

Gradual withdrawal should be considered in those whose disease is unlikely to relapse and who have:

- Recently received repeated courses (particularly courses of more than 3 weeks' duration)
- Taken a short course within 1 year of stopping long-term therapy
- Other possible causes of adrenal suppression
- Received more than 40 mg prednisolone (or equivalent) daily
- Been given repeat doses in the evening
- Received more than 3 weeks' treatment

Abrupt withdrawal may be considered in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above.

During corticosteroid withdrawal the dose may be reduced rapidly down to the physiological dosage (equivalent to 7.5 mg prednisolone daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

- **Hydrocortisone**

- **Dosage form**

- Injection: 100 mg/ml (sodium succinate), 25 mg/ml* (acetate) (see Section 3)

18.2 ANDROGENS

Androgens are secreted by the testes and also by the adrenal cortex and the ovaries. In the male, they are responsible for the development and maintenance of the sex organs and the secondary sexual characteristics, normal reproductive function, and sexual performance ability, in addition to stimulating the growth and development of the skeleton and skeletal muscle during puberty. At high doses in the normal male, androgens inhibit pituitary gonadotrophin secretion and depress spermatogenesis.

Testosterone is used as replacement therapy in those who are hypogonadal due to either pituitary (secondary hypogonadism) or testicular disease (primary hypogonadism). However, androgens are ineffective as treatment for impotence and impaired spermatogenesis unless there is associated hypogonadism; they should not, therefore, be given until the hypogonadism has been properly investigated. Treatment should always be under expert supervision. When androgens are given to patients with hypopituitarism, they can lead to normal sexual development and potency but not fertility. If fertility is desired, the usual treatment is with gonadotrophins or a pulsatile gonadotrophin-releasing hormone, which will stimulate spermatogenesis as well as androgen production. Androgens cannot induce fertility in men with primary hypogonadism. Caution should be exercised in treating boys with delayed puberty with excessive doses of testosterone since the fusion of epiphyses is hastened and this may result in short stature. Androgens, including testosterone, have been used in postmenopausal women for the palliative treatment of androgen-responsive, advanced metastatic breast cancer; care must be taken to prevent masculinizing effects.

18.3 CONTRACEPTIVES

18.3.1 Oral hormonal contraceptives

Hormonal contraception is one of the most effective methods of reversible fertility control.

Combined oral contraceptives

Estrogen-plus-progestogen combinations are the most widely used hormonal contraceptives. They produce a contraceptive effect mainly by suppressing the hypothalamic-pituitary system (resulting in prevention of ovulation), but also by causing changes in the endometrium that make it unreceptive to implantation.

Endometrial proliferation is usually followed by thinning or regression of the endometrium, resulting in reduced menstrual flow. Ovulation usually resumes within 3 menstrual cycles after oral contraception has been discontinued; anovulation and amenorrhea persisting for 6 months or longer requires investigation and appropriate treatment if necessary.

Potential non-contraceptive benefits of combined oral contraceptives include improved regularity of the menstrual cycle, decreased blood loss, reduced risk of iron-deficiency anemia, and a significant decrease in dysmenorrhea. Long-term use is associated with reduced risk of endometrial and ovarian cancer and of some pelvic infections.

There may be an association between the amount of estrogen and progestogen in combined oral contraceptives and the increased risk of adverse cardiovascular effects. The use of oral contraceptive combinations containing the progestogens desogestrel or gestodene is associated with a slightly increased risk of venous thromboembolism compared with oral contraceptives containing the progestogens **levonorgestrel** or **norethisterone**.

Risk factors for venous thromboembolism or arterial disease

Risk factors for *venous thromboembolism* include family history of venous thromboembolism in a first-degree relative aged under 45 years, obesity, long-term immobilization, and varicose veins.

Risk factors for *arterial disease* include family history of arterial disease in a first-degree relative aged under 45 years, diabetes mellitus, hypertension, smoking, age over 35 years (avoid if over 50 years), obesity, and migraine.

If any one of the above risk factors is present, combined oral contraceptives should be used with caution; if two or more factors for either venous thromboembolism or arterial disease are present, combined oral contraceptives should be avoided. Combined oral contraceptives are contraindicated in migraine with aura, in severe migraine without aura regularly lasting over 72 hours despite treatment, and in migraine treated with ergot derivatives.

Surgery

Estrogen-containing oral contraceptives should preferably be discontinued (and adequate alternative contraceptive arrangements made) 4 weeks before major elective surgery and before all surgery to the legs or surgery that involves prolonged immobilization of a lower limb. They should normally be restarted at the first menses occurring at least 2 weeks after full mobilization. When discontinuation is not possible, thromboprophylaxis (with heparin [Section 10.2] and graduated compression hosiery) is advised.

Reasons to stop combined oral contraceptives immediately

Combined estrogen-containing oral contraceptives should be stopped immediately if any of the following symptoms occur and should be resumed only after consultation with a health-care provider:

- Sudden severe chest pain (even if not radiating to left arm)
- Sudden breathlessness (or cough with blood-stained sputum)
- Severe pain in calf of one leg
- Severe stomach pain
- Serious neurological effects such as unusual, severe, prolonged headache (especially if first occurrence or headache are getting progressively worse) or sudden partial or complete loss of vision or sudden disturbance of hearing, or other perceptual disorders or dysphagia, or bad fainting attack or collapse, or first unexplained epileptic seizure or weakness, motor disturbances, or very marked numbness suddenly affecting one side or one part of body
- Hepatitis, jaundice, liver enlargement
- Blood pressure above 160 mmHg systolic and 100 mmHg diastolic
- Detection of two or more risk factors for venous thromboembolism or arterial disease (see note above)

- **Ethinylestradiol + levonorgestrel**

Ethinylestradiol with levonorgestrel is a representative combined oral contraceptive preparation. Various combinations can serve as alternatives.

- **Dosage form**

- Tablets: 0.03 mg + 0.15 mg and 0.05 mg + 0.25 mg

- **Uses**

- Contraception
- Menstrual symptoms
- Endometriosis (see *also* Section 18.7)

- **Contraindications**

- Administration within 3 weeks of birth
 - Breast-feeding (until weaning or for the first 6 months after birth):
Appendix C
 - Personal history of two or more risk factors for venous thromboembolism and arterial disease (see *also* note above)
 - 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 despite treatment or migraine treated with ergot derivatives (see *also* note below)
 - History of sub-acute bacterial endocarditis
 - Ischemic 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
 - Systemic lupus erythematosus
 - Liver adenoma
 - History of hemolytic uremic 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 (see *also* note above)

- Migraine without focal aura or controlled with 5HT1 agonist (see *also* note below)
- Hyperprolactinemia (seek specialist advice)
- Some types of hyperlipidemia
- Gallbladder disease
- History of severe depression especially if induced by hormonal contraception
- Long-term immobilization (see *also* note on Travel below)
- Sickle-cell disease
- Inflammatory bowel disease including Crohn's disease
- **Interactions:** Appendix A
- **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.

○ **Dose**

Contraception, by mouth

- **ADULT** (female): 1 tablet daily for 21 days; subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs)

Everyday (ED) preparations

- **ADULT** (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)

Administration: 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 (see note on Missed pill below).

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 (at 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 ED—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.

Effect of diarrhea and vomiting: Vomiting within 2 hours of taking an oral contraceptive or very severe diarrhea can interfere with the absorption of the pill. Additional precautions should be used during and for 7 days after recovery (see *also* note on Missed pill above). If vomiting and diarrhea 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).

- **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 tumors
- Breast cancer (studies have shown a small increase in risk of having breast cancer diagnosed in women using the combined oral contraceptive)
- This relative risk may be due to earlier diagnosis.
- Cancers diagnosed early are more likely to be localized to the breast.
- Risk appears to relate to the age at which the contraceptive is stopped rather than to the total duration of use.
- Any increased risk disappears gradually during the 10 years after stopping and there is no excess risk after 10 years.
- A small increase in the risk of breast cancer should be weighed against the protective effect (against cancers of the ovary and endometrium).

- **Ethinylestradiol + norethisterone**

Ethinylestradiol with norethisterone is a representative combined oral contraceptive preparation. Various combinations can serve as alternatives

- **Dosage form**

- Tablets: 0.035 mg + 1 mg

- **Uses**

- Contraception
 - Menstrual symptoms
 - Endometriosis (see *also* Section 18.7)

- **Contraindications**

- Administration within 3 weeks of birth
- Breast-feeding (until weaning or for the first 6 months after birth):
Appendix C
- Personal history of 2 or more risk factors for venous thromboembolism and arterial disease (see *also* note above)
- 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 despite treatment or migraine treated with ergot derivatives (see *also* note below)
- History of sub-acute bacterial endocarditis
- Ischemic 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
- Systemic lupus erythematosus
- Liver adenoma
- History of hemolytic uremic 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 (see *also* note above)
- Migraine without focal aura or controlled with 5HT1 agonist (see *also* note below)
- Hyperprolactinemia (seek specialist advice)
- Some types of hyperlipidemia
- Gallbladder disease
- History of severe depression especially if induced by hormonal contraception
- Long-term immobilization (see *also* note on Travel below)
- Sickle-cell disease
- Inflammatory bowel disease including Crohn's disease
- **Interactions:** Appendix A
- **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.

○ **Dose**

Contraception, by mouth

- **ADULT** (female): 1 tablet daily for 21 days; subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs)

Everyday (ED) preparations

- **ADULT** (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)

Administration: 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 (see note on Missed pill below).

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 (at 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 ED 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.

Effect of diarrhea and vomiting: Vomiting within 2 hours of taking an oral contraceptive or very severe diarrhea can interfere with the absorption of the pill. Additional precautions should be used during and for 7 days after recovery (see *also* note on Missed pill above). If vomiting and diarrhea 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).

- **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 tumors; breast cancer (studies have shown a small increase in risk of having breast cancer diagnosed in women using combined oral contraceptive)
- This relative risk may be due to earlier diagnosis.
- Cancers diagnosed early are more likely to be localized to the breast.
- Risk appears to relate to the age at which the contraceptive is stopped rather than to the total duration of use.
- Any increased risk disappears gradually during the 10 years after stopping and there is no excess risk after 10 years.
- A small increase in the risk of breast cancer should be weighed against the protective effect (against cancers of the ovary and endometrium).

- **Ethinylestradiol + norgestrel**

Ethinylestradiol with levonorgestrel is a representative combined oral contraceptive preparation. Various combinations can serve as alternatives.

- **Dosage form**

- Tablets: 0.03 mg + 0.3 mg (0.3 mg norgestrel is equivalent to 0.15 mg levonorgestrel)

- **Uses**

- *See under* Ethinylestradiol + levonorgestrel.

- **Contraindications**
 - *See under* Ethinylestradiol + levonorgestrel.
- **Precautions**
 - *See under* Ethinylestradiol + levonorgestrel.
- **Dose**
 - *See under* Ethinylestradiol + levonorgestrel.
- **Adverse effects**
 - *See under* Ethinylestradiol + levonorgestrel.
- **Levonorgestrel**

Levonorgestrel is a progestogen-only oral contraceptive.

 - **Dosage form**
 - Tablet: 0.03 mg
 - **Uses**
 - Contraception (particularly when estrogens are contraindicated)
 - Emergency hormonal contraception
 - **Contraindications**
 - *Contraception*: severe arterial disease
 - Liver tumors
 - History of breast cancer (may be used after 5 years if no evidence of current disease)
 - Thromboembolic disorders
 - Porphyria
 - ***Emergency contraception***: Porphyria

- **Precautions**

- Undiagnosed vaginal bleeding
- Cardiac disease
- Past ectopic pregnancy
- Active liver disease, recurrent cholestatic jaundice
- Migraine
- Diabetes mellitus; pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Dose**

Contraception, by mouth

- **ADULT** (female): 1 tablet (0.03 mg) daily, starting on day 1 of the cycle and then continuously

Administration: 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.

Effect of diarrhea and vomiting: Vomiting within 2 hours of taking an oral contraceptive or very severe diarrhea can interfere with the absorption of the pill. Additional precautions should be used during and for 2 days after recovery (see *also* note on Missed pill above).

Emergency (post-coital) contraception, by mouth

- **ADULT** (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
-
- **Adverse effects**
 - Menstrual irregularities (including oligomenorrhea and menorrhagia) usually resolve with long-term treatment.
 - Nausea, vomiting, headache, dizziness, breast discomfort, depression, skin disorders, disturbances of appetite, weight increase, change in libido
 - Breast cancer (studies have shown a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill)
 - This relative risk may be due to earlier diagnosis.
 - Risk appears to relate to the age at which the contraceptive is stopped rather than to the total duration of use.
 - Any increased risk disappears gradually during the 10 years after stopping and there is no excess risk after 10 years.
 - The small increase in the risk of breast cancer should be weighed against the benefits.

- **Norgestrel**

Norgestrel is a compound containing two stereoisomers, levonorgestrel and dextronorgestrel. Levonorgestrel is more used and two times as powerful as norgestrel. For example, 37.5 micrograms of levonorgestrel is equivalent to 75 micrograms of norgestrel. For indications, contraindications, precautions and adverse effects, see Levonorgestrel.

- **Dosage form**

- Tablet: 0.075 mg

18.3.2 Injectable hormonal contraceptives

Medroxyprogesterone acetate and **norethisterone enantate** are long-acting progestogens, which are given by intramuscular injection every 3 months and every 2 months, respectively. Women should be counseled about the likelihood of menstrual disturbance and the potential for a delay in return to full fertility; although delayed return of fertility and irregular cycles may occur after discontinuation of treatment with injectable progestogens, there is no evidence of permanent infertility. Heavy bleeding has been reported in patients given parenteral progestogen-only contraceptives in the immediate puerperium and thus the first dose is best delayed until 6 weeks after birth. If the woman is not breast-feeding, the first injection may be given within 5 days after birth but she should be warned that the risk of heavy or prolonged bleeding may be increased. Parenteral progestogen-only contraceptives reliably inhibit ovulation, as well as protect against ectopic pregnancy and functional ovarian cysts.

Reduction in bone-mineral density and rare cases of osteoporosis and osteoporotic fractures have been reported with medroxyprogesterone acetate; the reduction in bone-mineral density occurs in the first 2–3 years of use and then stabilizes.

- **Medroxyprogesterone acetate depot**
 - **Dosage form**
 - Depot injection: 150 mg/ml in 1 ml vial
 - **Uses**
 - Parenteral progestogen-only contraception (short- or long-term)
 - **Contraindications**
 - Pregnancy: Appendix B
 - 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: Appendix E
 - Severe arterial disease
 - Multiple risk factors for venous thromboembolism and arterial disease; porphyria
 - **Precautions**
 - Migraine
 - Liver disease: Appendix E
 - Thromboembolic or coronary vascular disease
 - Diabetes mellitus
 - Hypertension
 - Renal disease
 - **Interactions:** Appendix A
 - **Dose**

Contraception (short-term), by deep intramuscular injection

- **ADULT** (female): 150 mg within the first 7 days of cycle or within the first 5 days after parturition (delay until 6 weeks after parturition if breast-feeding)

Contraception (long-term), by deep intramuscular injection

- **ADULT** (female): As for short-term, repeated every 3 months

Administration: 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 counseling (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.

- **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; see *also* Adverse effects *under* Levonorgestrel in Section 18.3.1)

18.3.3 Intrauterine devices

Copper-bearing intrauterine contraceptive devices (IUDs) consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of copper. Smaller devices have

been introduced to minimize adverse effects and the replacement time for these devices is normally between 3 and 8 years. On this basis, and as fertility declines with age, an IUD fitted in a woman over 40 years of age may remain in the uterus until menopause.

The IUD (or “coil”) is appropriate for women who expect to use it for continuous long-term contraception. It is suitable for older parous women; IUDs should be used with caution in young nulliparous women because of the increased risk of expulsion. Young women at risk of sexually transmitted infections are also at risk of pelvic inflammatory disease.

The timing and technique of fitting an intrauterine device are critical for its performance and call for proper training and experience. Women should receive full counseling backed by the manufacturer’s approved leaflet. For routine contraception, the device can be inserted into the uterus between 4 and 12 days after the start of menstruation (see note below for use as emergency contraception). There is an increased risk of infection for 20 days after insertion; however, the increased risk may be related to undetected preexisting lower genital tract infections. Prescreening (at least for chlamydia and gonorrhea) should be performed if feasible and appropriate. If sustained pelvic or lower abdominal pain occur during the 20 days following insertion of the device, the woman should be treated as having acute pelvic inflammatory disease.

An IUD should not be removed in mid-cycle unless an additional contraceptive was used for the previous 7 days. If removal is essential (for example, to treat severe pelvic infection), post-coital contraception should be considered. If the woman becomes pregnant, the device should be removed in the first trimester and the possibility of ectopic pregnancy considered; if the threads of the intrauterine device are already missing on presentation, the pregnancy is at risk of second-trimester abortion, hemorrhage, preterm delivery, and infection.

Emergency contraception. Insertion of a copper intrauterine contraceptive device is more effective than hormonal methods of emergency contraception; the device can be inserted at any time in the menstrual cycle within 5 days of unprotected intercourse. Sexually transmitted diseases should be excluded and insertion of the device should usually be covered by antibacterial prophylaxis

- **Copper-containing device**

- **Uses**

- Contraception
 - Emergency contraception

- **Contraindications**

- Pregnancy
 - Severe anemia
 - 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 tuberculosis
 - Unexplained uterine bleeding
 - Active trophoblastic disease
 - Distorted or small uterine cavity
 - Copper allergy
 - Wilson's disease
 - Medical diathermy

- **Precautions**

- Anemia

- Heavy menstrual bleeding, endometriosis, severe primary dysmenorrhea, 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
- Gynecological 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))

○ **Administration**

Contraception

- **ADULT** (female): Insert device at any time between day 4 and day 12 after the start of menstrual bleeding; do not fit during heavy menstrual bleeding.

Emergency contraception

- **ADULT** (female): Insert device 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; the device can be removed at the beginning of menstruation if no longer required.

○ **Adverse effects**

- Uterine or cervical perforation, displacement, expulsion
- Exacerbation of pelvic infection
- Heavy menstrual bleeding

- Dysmenorrhea
- Pain and bleeding and occasionally epileptic seizure or vasovagal attack on insertion

18.3.4 Barrier methods

Barrier methods are not as effective in preventing conception as hormonal contraception and copper intrauterine devices. Spermicidal methods when used alone are generally considered to be relatively ineffective and such use is not recommended.

- **Barriers: male latex condom, male non-latex condom, or female non-latex condom; diaphragm or cervical cap**
 - **Uses**
 - Contraception
 - For condoms, also to decrease risk of transmission of HIV and other sexually transmitted diseases
 - **Precautions**
 - Oil-based products such as baby oil, massage oil, lipstick, petroleum jelly, suntan oil can damage latex condoms and render them less effective as a barrier method of contraception and as a protection from sexually transmitted infections, including HIV—if a lubricant is required, a water-based one should be used.
 - Male condom must be put on before the penis touches the vaginal area and the penis must not touch the vaginal area after the condom has been taken off.
 - Spermicides and diaphragm are not suitable for women with or at high risk of HIV infection.
 - **Adverse effects**

- Vaginal and cervical irritation (spermicides), toxic shock syndrome (diaphragm, cap)

18.4 ESTROGENS

Estrogens are necessary for the development of female secondary sexual characteristics; they also stimulate myometrial hypertrophy and endometrial hyperplasia. They affect bone density by increasing calcium deposition. They are secreted at varying rates during the menstrual cycle throughout the period of activity of the ovaries. During pregnancy, the placenta becomes the main source of estrogens. Ovarian secretion declines at menopause.

Estrogen therapy is given cyclically or continuously principally for contraception and for the alleviation of menopausal symptoms. If long-term therapy is required for menopausal symptoms, a progestogen should normally be added to prevent cystic hyperplasia of the endometrium (or of endometrial foci in women who have had a hysterectomy) and possible transformation to cancer.

The palliative care of advanced inoperable, metastatic carcinoma of the breast in both men and postmenopausal women is another indication for estrogen therapy.

Risks of Hormone Replacement Therapy

When prescribing hormone replacement therapy (HRT), it is necessary to make women aware of the increased incidence of *venous thromboembolism*, of *stroke* and, after some years of use, of *endometrial cancer* (reduced by a progestogen) and *breast cancer*. Each decision to start HRT should be made on an individual basis, and treatment should be regularly reappraised. Factors such as concomitant corticosteroid therapy, family history of osteoporosis, thinness, level of exercise, alcoholism or smoking, early menopause, and fractures to the hip or forearm before the age of 65 years should be taken into account when considering the use of HRT.

- **Ethinylestradiol**

Ethinylestradiol is a representative estrogen. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 0.01 mg and 0.05 mg

- **Uses**

- Hormone replacement for menopausal symptoms (in combination with a progestogen, if necessary)
- Osteoporosis prophylaxis
- Palliation in prostate cancer
- Contraception in combination with a progestogen (Section 18.3.1)

- **Contraindications**

- Pregnancy: Appendix B
- Estrogen-dependent cancer
- Active thrombophlebitis or thromboembolic disorders or history of recent venous thromboembolism (unless already on anticoagulant therapy)
- Undiagnosed vaginal bleeding
- Breast-feeding: Appendix C
- Liver disease, Dubin-Johnson and Rotor syndromes (where liver function tests have failed to return to normal; or monitor closely)

- **Precautions**

- Migraine (or migraine-like headache)
- Diabetes mellitus (increased risk of heart disease)
- History of breast nodules or fibrocystic disease (increased risk of breast cancer; closely monitor breast status)

- Uterine fibroids may increase in size.
- Symptoms of endometriosis may be exacerbated.
- Predisposition to thromboembolism (*see also* introductory note above)
- Presence of antiphospholipid antibodies
- Increased risk of gallbladder disease
- Hypophyseal tumors; porphyria
- **Interactions:** Appendix A

○ **Dose**

Hormone replacement, by mouth

- **ADULT** (female): 10–20 micrograms daily (with a progestogen if necessary; *see* introductory note above)

Palliation in prostate cancer, by mouth

- **ADULT** (male): 0.15–1.5 mg daily

○ **Adverse effects**

- Nausea and vomiting, abdominal cramps and bloating, weight increase
- Breast enlargement and tenderness
- Premenstrual-like syndrome
- Sodium and fluid retention; thromboembolism (*see also* introductory note above)
- Altered blood lipids (may lead to pancreatitis)
- Cholestatic jaundice, glucose intolerance
- Rash and chloasma
- Changes in libido
- Depression, headache, migraine, dizziness, leg cramps (rule out venous thrombosis)
- Vaginal candidiasis

- Contact lenses may irritate.

18.5 INSULINS AND OTHER ANTIDIABETIC AGENTS

Diabetes mellitus is characterized by hyperglycemia and disturbances of carbohydrate, fat, and protein metabolism. There are two principal types of diabetes.

Type 1 diabetes or *insulin-dependent diabetes mellitus* is due to a deficiency of insulin caused by autoimmune destruction of pancreatic beta cells. Patients require administration of insulin.

Type 2 diabetes or *non-insulin-dependent diabetes mellitus* is due either to reduced secretion of insulin from the pancreas or to peripheral resistance to the action of insulin.

The aim of treatment is to achieve the best possible control of blood glucose concentration and prevent or minimize complications including microvascular complications such as retinopathy, albuminuria, and neuropathy. Diabetes mellitus is a strong risk factor for cardiovascular disease; other risk factors for cardiovascular disease, such as smoking, hypertension, obesity, and hyperlipidemia, should also be addressed.

Insulin

Insulin preparations can be classified according to duration of action after subcutaneous injection as follows:

- Those of short duration, which have a relatively rapid onset of action—for example, soluble or neutral insulin
- Those with an intermediate action—for example, isophane insulin
- Those with a relatively slow onset and long duration of action—for example, protamine zinc insulin

Oral antidiabetic drugs

Oral antidiabetic (hypoglycemic) drugs are used for non-insulin-dependent diabetes mellitus in patients who do not respond to dietary adjustment and an increase in physical exercise. They are used to supplement the effects of diet and exercise, not to replace them. There are various types of oral antidiabetic agents, the most commonly used being the sulfonylureas and the biguanide metformin.

Sulfonylureas act mainly by augmenting insulin secretion and are therefore only effective if there is some residual pancreatic beta-cell activity. They may occasionally lead to hypoglycemia 4 hours or more after food. This usually indicates excessive dosing and tends to occur more frequently in the elderly and with the long-acting sulfonylureas, such as **glibenclamide**. The sulfonylureas have the disadvantage that they may encourage weight gain. They should not be used during breast-feeding, and caution is required in the elderly and those with renal or hepatic insufficiency because of the risk of hypoglycemia. Insulin therapy is generally required during intercurrent illness (such as myocardial infarction), coma, infection, and trauma, and also during surgery and pregnancy.

Metformin exerts its effect by decreasing gluconeogenesis and by increasing peripheral utilization of glucose. Metformin can act only in the presence of endogenous insulin, and therefore is effective only in diabetics with some residual functioning pancreatic islet cells. It is used as a first-line treatment in overweight non-insulin-dependent diabetic patients and in those for whom strict dieting and sulfonylureas have failed to control their disease. One major advantage of metformin is that it does not usually cause hypoglycemia. During medical and surgical emergencies, insulin treatment is almost always required; insulin should be substituted for metformin before elective surgery and in pregnancy.

Treatment of hypoglycemia

Hypoglycemia is a potential complication in all patients treated with insulin or less frequently with sulfonylureas. The consequences of hypoglycemia include confusion, seizures, coma, and cerebral infarction.

Oral glucose, 10–20 grams, is given orally to hypoglycemic patients. Ten grams of blood glucose can be achieved with taking 2 teaspoons of sugar. If required, this amount can be repeated after 10–15 minutes.

Emergency care is required if hypoglycemia causes unconsciousness and oral glucose is not tolerated or cannot be administered; use injectable glucagon and have patient start taking carbohydrates as soon as possible in order to recover hepatic glycogen levels. An alternative is to administer 50 ml 20% glucose through intravenous infusion with a syringe having a large needle in one of the largest body veins. Administer with caution because glucose with such concentration is irritating (especially prevent entering glucose beneath the skin). As an alternative, 25 ml of 50% glucose can be used intravenously through infusion, but this amount is very thick. Ten percent glucose of high volumes can also be used through intravenous infusion. If the administration of intravenous glucose is not possible, glucagon (a hormone which increases blood glucose levels) can be used.

- **Glibenclamide**
 - **Dosage form**
 - Tablet: 5 mg
 - **Uses**
 - Diabetes mellitus
 - **Contraindications**
 - Ketoacidosis

- Porphyria
- Breast-feeding: Appendix C
- **Precautions**
 - Pregnancy: Appendix B
 - Renal impairment: Appendix D
 - Hepatic impairment: Appendix E
 - Elderly (reduce dose)
 - Substitute insulin during intercurrent illness including severe infection, trauma, surgery, and pregnancy (see *also* introductory note above)
 - **Interactions:** Appendix A
- **Dose**

Diabetes mellitus, by mouth

 - **ADULT:** Initially 5 mg once daily with or immediately after breakfast (2.5 mg in the elderly), adjusted according to response (max. 15 mg daily)
- **Adverse effects**
 - Gastrointestinal disturbances and headache (usually mild and infrequent), liver disorders
 - Hypersensitivity reactions (usually only in first 6–8 weeks)
 - Rarely erythema multiforme, exfoliative dermatitis, fever, and jaundice
 - Hypoglycemia, particularly in the elderly
 - Rarely blood disorders including leukopenia, thrombocytopenia, agranulocytosis, pancytopenia, hemolytic anemia, and aplastic anemia

- **Intermediate-acting insulin**

- **Dosage form**

- Injection: 40 IU/ml in 10 ml vial; 100 IU/ml in 10 ml vial (as compound insulin zinc suspension or isophane insulin)

- **Uses**

- Diabetes mellitus

- **Contraindications**

- Intravenous administration

- **Precautions**

- See note above.
 - Renal impairment (reduce dose): Appendix D
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A

- **Dose**

Diabetes mellitus, by subcutaneous injection

- **ADULT** and **CHILD:** According to individual requirements (*see also* introductory note above)

- **Adverse effects**

- Hypoglycemia in overdose
 - Rarely hypersensitivity reactions, including urticaria and rash
 - Local reactions and lipoatrophy at injection site

- **Insulin injection (soluble)**

- **Dosage form**

- Injection: 40 IU/ml in 10 ml vial; 100 IU/ml in 10 ml vial

- **Uses**

- Diabetes mellitus
- Diabetic emergencies and during surgery
- Diabetic ketoacidosis or coma

- **Precautions**

- See note above.
- Renal impairment (reduce dose): Appendix D
- Pregnancy (Appendix B)
- Breast-feeding (Appendix C)
- **Interactions:** Appendix A

- **Dose**

Diabetes mellitus, by subcutaneous injection, by intramuscular injection, by intravenous injection or by intravenous infusion

- **ADULT** and **CHILD:** According to individual requirements (see *also* introductory notes above)

- **Adverse effects**

- Transient edema
- Hypoglycemia in overdose
- Rarely hypersensitivity reactions including urticaria and rash
- Local reactions and lipoatrophy at injection site

- **Metformin**

- **Dosage form**

- Tablets: 500 mg, 750 mg,* and 1 g* (hydrochloride)

- **Uses**
 - Diabetes mellitus
- **Contraindications**
 - Renal impairment: Appendix D
 - Ketoacidosis
 - Risk of tissue hypoxia, caused by, for example, sepsis, respiratory failure, recent myocardial infarction, or hepatic impairment (withdraw treatment)
 - Use of iodine-containing X-ray contrast media (do not restart metformin until renal function returns to normal)
 - Use of general anesthesia (suspend metformin on the morning of surgery and restart when renal function returns to normal)
 - Alcohol dependence
 - Pregnancy: Appendix B
- **Precautions**
 - Monitor renal function before treatment and once or twice annually (more frequently in the elderly or if deterioration suspected).
 - Substitute insulin during severe infection, trauma, surgery and pregnancy (*see also* introductory note above).
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A
- **Dose**

Diabetes mellitus, by mouth

- **ADULT** and **CHILD** over 10 years: Initially 500 mg with breakfast for at least 1 week, then 500 mg with breakfast and evening meal for at least 1 week, then 500 mg with breakfast, lunch, and evening

meal or 850 mg every 12 hours with or after food; usual maximum 2 g daily in divided doses

- **Adverse effects**

- Anorexia, nausea and vomiting, diarrhea (usually transient), abdominal pain, metallic taste
- Rarely lactic acidosis (most likely in patients with renal impairment; discontinue)
- Decreased vitamin B12 absorption, erythema, pruritus, and urticaria
- Hepatitis also reported

18.6 OVULATION INDUCERS

The anti-estrogen **clomifene** is used in the treatment of female infertility due to disturbances in ovulation. It induces gonadotrophin release by occupying estrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms. Patients should be carefully counseled and should be made fully aware of the potential adverse effects, including a risk of multiple pregnancy (rarely, more than twins), of this treatment. Most patients who are going to respond to treatment will do so to the first course; three courses should be adequate. Long-term cyclical therapy (more than six cycles) is not recommended as it may increase the risk of ovarian cancer.

- **Clomifene**

Clomifene citrate is a complementary list medicine for fertility treatment.

- **Dosage form**

- Tablets: 25 mg* and 50 mg (citrate)

- **Uses**

- Anovulatory infertility

- **Contraindications**

- Hepatic disease: Appendix E
- Ovarian cysts
- Hormone-dependent tumors or uterine bleeding of undetermined cause
- Pregnancy (exclude before treatment): Appendix B)

- **Precautions**

- Visual disturbances (discontinue and initiate eye examination) and 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)
- Breast-feeding: Appendix C

- **Dose**

Anovulatory infertility, by mouth

- **ADULT** (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.

- **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

18.7 PROGESTOGENS

Progesterone is a hormone secreted by the corpus luteum whose actions include induction of secretory changes in the endometrium, relaxation of the uterine smooth muscle, and production of changes in the vaginal epithelium.

Progesterone is relatively inactive following oral administration and produces local reactions at the site of injection. This has led to the development of synthetic progestogens including levonorgestrel, **norethisterone**, and **medroxyprogesterone**.

- **Norethisterone**

- **Dosage form**

- Tablet: 5 mg

- **Uses**

- Endometriosis
- Menorrhagia
- Severe dysmenorrhea
- Contraception (Section 18.3.2)
- Hormone replacement therapy (Section 18.4)

- **Contraindications**

- Pregnancy: Appendix B
 - Undiagnosed vaginal bleeding
 - Hepatic impairment or active liver disease: Appendix E
 - Severe arterial disease
 - Breast or genital tract cancer; porphyria
 - History of idiopathic jaundice, severe pruritus, or pemphigoid gestationis in pregnancy
- **Precautions**
 - Epilepsy
 - Migraine
 - Diabetes mellitus
 - Hypertension; cardiac or renal disease: Appendix D
 - Those susceptible to thromboembolism
 - Depression
 - Breast-feeding: Appendix C
 - ***Interactions:*** Appendix A
 - **Dose**

Endometriosis, by mouth

- **ADULT** (female): 10 mg daily starting on day 5 of cycle (increased to 20–25 mg daily if spotting occurs, reduced once bleeding has stopped)

Menorrhagia, by mouth

- **ADULT** (female): 5 mg 3 times daily for 10 days to stop bleeding; followed by 5 mg twice daily from day 19 to day 26 of cycle to prevent bleeding

Dysmenorrhea, by mouth

- **ADULT** (female): 5 mg 2–3 times daily from day 5 to day 24 for 3–4 cycles

- **Adverse effects**

- Acne
- Urticaria
- Fluid retention
- Weight increase
- Gastrointestinal disturbances
- Changes in libido
- Breast discomfort
- Premenstrual symptoms, irregular menstrual cycles
- Depression
- Insomnia, somnolence
- Headache, dizziness
- Alopecia
- Hirsutism
- Anaphylactoid-like reactions
- Exacerbation of epilepsy and migraine
- Rarely jaundice

18.8 THYROID HORMONES AND ANTITHYROID MEDICINES

Thyroid hormones

Thyroid agents are natural or synthetic agents containing levothyroxine (thyroxine) or liothyronine (tri-iodothyronine). Their principal effect is to increase the metabolic rate. They also exert a cardiostimulatory effect, which may be the result of a direct action on the heart.

Thyroid hormones are used in hypothyroidism (myxedema) and also in diffuse non-toxic goiter, Hashimoto thyroiditis (lymphadenoid goiter) and thyroid carcinoma. Neonatal hypothyroidism requires prompt treatment for normal development.

Levothyroxine sodium (thyroxine sodium) is the treatment of choice for maintenance therapy. It is almost completely absorbed from the gastrointestinal tract but the full effects are not seen until up to 1–3 weeks after beginning therapy; there is a slow response to dose change and effects may persist for several weeks after withdrawal. Dosage of levothyroxine in infants and children for congenital hypothyroidism and juvenile myxedema should be titrated according to clinical response, growth assessment, and measurement of plasma thyroxine and thyroid-stimulating hormone.

Antithyroid medicines

Antithyroid drugs such as propylthiouracil and **carbimazole** are used in the management of thyrotoxicosis. They are also used to prepare the patient for thyroidectomy. They are usually well tolerated, with mild leukopenia or rashes developing in only a small percentage of cases, usually during the first 6–8 weeks of therapy. During this time, the blood count should be checked every 2 weeks or if a sore throat or other signs of infection develop. The drugs are generally given in a high dose in the first instance until the patient becomes euthyroid; the dose may then be gradually reduced to a maintenance dose that is continued for 12–18 months, followed by monitoring to identify relapse.

If necessary, treatment can be given in pregnancy, but antithyroid drugs cross the placenta and in high doses may cause fetal goiter and hypothyroidism. The lowest dose that will control the hyperthyroid state should be used.

Propylthiouracil appears in breast milk but its use does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used.

If surgery (partial thyroidectomy) is contemplated, it may be necessary to give **potassium iodine** for 10–14 days in addition to antithyroid drugs to assist control and reduce vascularity of the thyroid. Potassium iodine should not be

used for long-term treatment since its antithyroid action tends to diminish. In patients in whom drug therapy fails to achieve long-term remissions, definitive treatment with surgery or (increasingly) radioactive iodine is preferable.

- **Carbimazole**

- **Dosage form**

- Tablet: 5 mg

- **Uses**

- Hyperthyroidism

- **Contraindications**

- Severe blood disorders

- **Precaution**

- Hepatic impairment: Appendix E
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C

- **Dose**

- **ADULT:** Carbimazole is given in a dose of 15–40 mg daily; higher doses should be prescribed under specialist supervision only.
 - **ADULT:** This dose is continued until the patient becomes euthyroid, usually after 4–8 weeks and the dose is then gradually reduced to a maintenance dose of 5–15 mg.
 - **ADULT:** Therapy is usually given for 12–18 months.
 - **CHILD:** 250 micrograms/kg 3 times daily according to patient response. Treatment should be done under supervision of a specialist.

Hyperthyroidism (including Graves' disease), by mouth

- **NEONATE:** Initially 750 micrograms/kg daily in single or divided doses until euthyroid (4–8 weeks), then gradually reduced 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.
- **CHILD 1 month–12 years:** Initially 750 micrograms/kg (max. 30 mg) daily in single or divided doses until euthyroid, then gradually reduced to a maintenance dose of 30–60% of the initial dose; higher initial doses occasionally required, particularly in thyrotoxic crisis
- **CHILD 12–18 years:** Initially 30 mg daily in single or divided doses until euthyroid, then gradually reduced to a maintenance dose of 30–60% of the initial dose; higher initial doses occasionally required, particularly in thyrotoxic crisis

Patient advice: Warn child and carers to tell doctor immediately if sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness develops.

- **Adverse effects**
 - Nausea, mild gastrointestinal disturbances, taste disturbance, headache
 - Fever, malaise
 - Rash, pruritus, arthralgia
 - Rarely myopathy, alopecia, bone marrow suppression (including pancytopenia and agranulocytosis)
- **Levothyroxine**
 - **Dosage form**
 - Tablets: 0.05 mg and 0.1 mg (sodium salt)

- **Uses**
 - Hypothyroidism
- **Contraindications**
 - Thyrotoxicosis
- **Precautions**
 - Cardiovascular disorders (myocardial insufficiency or myocardial infarction)
 - Hypopituitarism or predisposition to adrenal insufficiency (must be corrected by a corticosteroid prior to treatment with levothyroxine)
 - Elderly; long-standing hypothyroidism
 - Diabetes insipidus or diabetes mellitus (may need to increase dose of insulin or oral antidiabetic drug)
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - ***Interactions:*** Appendix A
- **Dose**

Hypothyroidism, by mouth

- **ADULT:** Initially 50–100 micrograms daily (25–50 micrograms for those over 50 years) before breakfast, increased by 25–50 micrograms every 3–4 weeks until normal metabolism maintained
- **ADULT** (maintenance): 100–200 micrograms daily (in cardiac disease, initially 25 micrograms daily or 50 micrograms on alternate days, adjusted in steps of 25 micrograms every 4 weeks)

Congenital hypothyroidism and juvenile myxedema (see also introductory note above), by mouth

- **NEONATE:** Up to 1 month, initially 5–10 micrograms/kg daily (5 micrograms/kg daily in infants and children over 1 month), adjusted

in steps of 25 micrograms every 2–4 weeks, until mild toxic symptoms appear, then reduce dose slightly

- **Adverse effects (usually with excessive dose)**

- Anginal pain, arrhythmias, palpitations, tachycardia
- Skeletal muscle cramps
- Diarrhea
- Vomiting
- Tremors
- Restlessness, excitability, insomnia
- Headache
- Flushing, sweating
- Excessive weight loss and muscular weakness

- **Potassium iodide**

- **Dosage form**

- Tablet: 60 mg
- Oral solution: 1 g/ml

- **Uses**

- Thyrotoxicosis (preoperative treatment)
- Sporotrichosis, subcutaneous phycomycosis (Section 6.3)

- **Contraindications**

- Breast-feeding: Appendix C
- Long-term treatment

- **Precautions**

- Pregnancy: Appendix B
- Children

- **Dose**

Preoperative management of thyrotoxicosis, by mouth

- **ADULT:** 60–180 mg daily

- **Adverse effects**

- Hypersensitivity reactions including coryza-like symptoms, headache, lacrimation, conjunctivitis, pain in salivary glands, laryngitis, bronchitis, and rash
- On prolonged treatment, depression, insomnia, and impotence; goiter in infants of mothers taking iodides

SECTION 19: Immunologicals

ACTIVE IMMUNITY

Active immunity may be induced by the administration of microorganisms or their products, which act as antigens to induce antibodies to confer a protective immune response in the host. Vaccination may consist of

- (a) A live, attenuated form of a virus or bacteria
- (b) Inactivated preparations of the virus or bacteria
- (c) Extracts of, or detoxified, exotoxins

Live, attenuated vaccines usually confer immunity with a single dose that is of long duration. Inactivated vaccines may require a series of injections in the first instance to produce an adequate antibody response, and in most cases require reinforcing (booster) doses. The duration of immunity varies from months to many years. Extracts of, or detoxified, exotoxins require a primary series of injections followed by reinforcing doses.

PASSIVE IMMUNITY

Passive immunity is conferred by injecting preparations made from the plasma of immune individuals with adequate levels of antibody to the disease for which protection is sought. Treatment has to be given soon after exposure to be effective. This immunity lasts only a few weeks but passive immunization can be repeated when necessary.

19.1 DIAGNOSTIC AGENTS

A positive tuberculin test indicates previous exposure to mycobacterial antigens through infection with one of the tubercle bacilli, or bacillus Calmette–Guérin (BCG) vaccination. However, the tuberculin test has limited diagnostic value. It does not distinguish between tuberculosis and other mycobacterial infections,

between active and quiescent disease, or between acquired infection and seroconversion induced by BCG vaccination.

- **Tuberculin, purified protein derivative (PPD)**
 - **Dosage form**
 - Injection: 10 IU/ml and 100 IU/ml
 - **Uses**
 - Test for hypersensitivity to tuberculo-protein
 - **Contraindications**
 - Should not be used within 4 weeks of receiving a live viral vaccine
 - **Precautions**
 - Elderly
 - Malnutrition
 - Viral or bacterial infections (including HIV and severe tuberculosis)
 - Malignant disease
 - Corticosteroid or immunosuppressant therapy (diminished sensitivity to tuberculin)
 - Avoid contact with open cuts, abraded or diseased skin, eyes, mouth

Note: National recommendations may vary.

- **Dose**

Test for hypersensitivity to tuberculo-protein, by intradermal injection

- **ADULT** and **CHILD:** 5 or 10 IU (1 unit in hypersensitive patients or if tuberculosis is suspected)

- **Administration**
 - According to manufacturer's directions
- **Adverse effects**
 - Occasionally nausea, headache, malaise, rash; immediate local reactions (more common in atopic patients)
 - Rarely vesicular or ulcerating local reactions, regional adenopathy, and fever

19.2 SERA AND IMMUNOGLOBULINS

Antibodies of human origin are usually termed *immunoglobulins*. Material prepared from animals is called *antiserum*. Because of serum sickness and other allergic-type reactions that may follow injections of antisera, this therapy has been replaced wherever possible by the use of immunoglobulins.

All immunoglobulins and antisera should comply with WHO requirements for blood and plasma products.

Contraindications and precautions

Anaphylaxis, although rare, can occur, and epinephrine (adrenaline) must always be immediately available during immunization (see Section 3).

Immunoglobulins may interfere with the immune response to live virus vaccines, which should be given either at least 3 weeks before or at least 3 months after administration of an immunoglobulin.

Adverse reactions

Local reactions, including pain and tenderness, may occur at the site of an *intramuscular injection*. Hypersensitivity reactions may also occur, including, rarely, anaphylaxis. Following an *intravenous injection*, systemic reactions, including fever, chills, facial flushing, headache, and nausea may occur,

particularly following high rates of infusion. Hypersensitivity reactions may also occur, including, rarely, anaphylaxis.

- **Anti-D immunoglobulin (human)**

Anti-D immunoglobulin is prepared from plasma with a high titer of anti-D antibody. It is available to prevent a rhesus-negative mother from forming antibodies to fetal rhesus-positive cells, which may pass into the maternal circulation. The aim is to protect any subsequent child against hemolytic disease of the newborn. It should be administered following any potentially sensitizing episode (for example, abortion, miscarriage, or stillbirth), ideally immediately or within 72 hours of the episode; however, even if a longer period has elapsed, it may still give protection and should be used. The anti-D immunoglobulin given depends on the level of exposure to rhesus-positive blood. The injection of anti-D immunoglobulin is not effective once the mother has formed anti-D antibodies. It is also given following transfusion of Rh0(D) incompatible blood.

Plasma fractions should comply with the *Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives* (Revised 1992), WHO Technical Report Series No 840, 1994, Annex 2.

- **Dosage form**

- Injection: 250 micrograms in single-dose vial

- **Uses**

- Prevention of formation of antibodies to rhesus-positive blood cells in rhesus-negative patients

- **Contraindications**

- See introductory notes.

- Known hypersensitivity to anti-D immunoglobulin
- **Precautions**
 - See introductory notes.
 - Rhesus-positive patients receiving treatment for blood disorders
 - Rhesus-negative patients with anti-D antibodies in their serum
 - **Interactions:** Appendix A

Rubella vaccine: Rubella vaccine may be administered in the postpartum period at the same time as anti-D immunoglobulin, but only if separate syringes and contralateral sites are used. If blood is transfused, the antibody response to the vaccine may be inhibited (measure rubella antibodies after 8 weeks and revaccinate if necessary).

- **Dose**

Following birth of a rhesus-positive infant to a rhesus-negative mother, by intramuscular injection

- **ADULT:** 250 micrograms immediately or within 72 hours of birth (see also introductory note above)

Following any potentially sensitizing episode (for example, amniocentesis, stillbirth), by intramuscular injection

- **ADULT:** Up to 20 weeks' gestation, 250 micrograms per episode (after 20 weeks, 500 micrograms) immediately or within 72 hours (see also introductory note above)

Following any potentially sensitizing episode (for example, amniocentesis, stillbirth), by intramuscular injection

- **ADULT:** 10–20 micrograms per ml transfused rhesus-positive blood

- **Adverse effects**

- See introductory notes.

- **Antitetanus immunoglobulin (human)**

Antitetanus immunoglobulin of human origin is a preparation containing immunoglobulins derived from the plasma of adults immunized with tetanus toxoid. It is used for the management of tetanus-prone wounds in addition to wound cleaning and, if appropriate, antibacterial prophylaxis and adsorbed tetanus vaccination (see Section 19.3).

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 Technical Report Series No 840, 1994, Annex 2.

- **Dosage form**

- Injection: 250 IU/ml, 500 IU/ml, 1500 IU/ml and 3,000 IU/ml

- **Uses**

- Passive immunization against tetanus as part of the management of tetanus-prone wounds

- **Contraindications**

- See introductory notes.

- **Precautions**

- See introductory notes.

Tetanus vaccine: If schedule requires tetanus vaccine and antitetanus immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites.

- **Dose**

Management of tetanus-prone wounds, by intramuscular injection

- **ADULT** and **CHILD**: 250 IU, increased to 500 IU if wound older than 24 hours or there is risk of heavy contamination, or following burns (see *also* Section 19.3)

- **Adverse effects**

- See introductory notes.

- **Diphtheria antitoxin**

Diphtheria antitoxin is prepared from the plasma or serum of healthy horses immunized against diphtheria toxin or diphtheria toxoid. It is used for passive immunization in suspected cases of diphtheria without waiting for bacterial confirmation of the infection. A test dose should be given initially to exclude hypersensitivity. Diphtheria antitoxin is not used for prophylaxis of diphtheria because of the risk of hypersensitivity.

- **Dosage form**

- Injection: 10,000 IU and 20,000 IU in vial

- **Uses**

- Passive immunization in suspected cases of diphtheria

- **Precautions**

- Initial test dose to exclude hypersensitivity
- Observation required after full dose (epinephrine (adrenaline) and resuscitation facilities should be available)

- **Dose**

Passive immunization in suspected diphtheria (see Precautions), by intramuscular injection

- **ADULT** and **CHILD**: 10,000–30,000 IU in mild-to-moderate cases
- 40,000–100,000 IU in severe cases (doses of more than 40,000 IU should be given in divided doses, the first portion by intramuscular injection, followed by the bulk of the dose by intravenous injection after an interval of 0.5–2 hours)

- **Adverse effects**

- Anaphylaxis with urticaria, hypotension, dyspnea, and shock
- Serum sickness up to 12 days after injection

- **Rabies immunoglobulin**

Rabies immunoglobulin is a preparation containing immunoglobulins derived from the plasma of adults immunized with rabies vaccine. It is used as part of the management of potential rabies following exposure of an unimmunized individual to an animal in or from a high-risk country. It should be administered as soon as possible after exposure without waiting for confirmation that the animal is rabid. The site of the bite should be washed with soapy water and the rabies immunoglobulin should be infiltrated in and around the site of the bite. In addition, rabies vaccine (see Section 19.3) should be administered at a different site.

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 Technical Report Series No 840, 1994, Annex 2.

- **Dosage form**

- Injection: 150 IU/ml in vial

- **Uses**
 - Passive immunization either post-exposure or in suspected exposure to rabies in high-risk countries in unimmunized individuals (in conjunction with rabies vaccine)
- **Contraindications**
 - See introductory notes.
 - Also avoid repeat doses after vaccine treatment initiated.
 - Intravenous administration
- **Precautions**
 - See introductory notes.

Rabies vaccine: If schedule requires rabies vaccine and rabies immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites.

- **Dose**

Passive immunization against rabies (post-exposure or following suspected exposure) by infiltration

- **ADULT** and **CHILD:** 20 IU/kg in and around the cleansed wound
- If wound is not visible or has healed, or if infiltration of whole volume is not possible, give remainder by intramuscular injection into the anterolateral thigh

- **Adverse effects**
 - See introductory notes.

- **Scorpion antivenom**

Scorpion antivenom are antibodies made against protein that exists in the venom of scorpions (these antibodies are extracted from serum of goat). As composition and types of protein in the venom of scorpion differs due to different species of scorpions (more than 1,500 species are recognized in the world), relevant antivenom should be used for those bitten by a scorpion. The most widely available species in Asian countries are *buthotus* and *centruroides*.

- **Dosage form**

- Injection: 5 ml vial containing scorpion antivenom immunoglobulin

- **Uses**

- Treatment of scorpion bite

- **Dose**

- 1 vial antivenom should be diluted in 100 ml of saline and administered *intravenously* in 30 minutes.
- If symptoms persist, a second vial can be administered in the same way as the first, after 1–3 hours.

- **Note**

- Test antivenom for sensitivity before administration.

Adjunctive treatment: Consider the following measures:

- Sterilize the bitten area with antiseptics and if needed administer tetanus antitoxin for prevention.
- Keep respiratory tract open and give artificial breathing if needed.
- Administer oxygen to patient if needed.
- Administer atropine if secretions in mouth and respiratory tract increase.

- Check blood pressure and if needed, administer blood pressure–regulating drugs.
 - Treat with anticonvulsive drugs (especially benzodiazepines) if patient develops convulsions.
 - Do not suck bitten area.
 - If needed, apply cold compress periodically for 1–2 minutes after every 15 minutes.
 - If pain exists, administer non-steroidal painkillers (morphine or fentanyl).
 - Administer antihistaminic drugs (H1 receptor blocker).
- **Contraindication**
 - Allergy to antivenom
 - **Precautions**
 - Breast-feeding: Appendix C
 - Pregnancy: Appendix B

19.3 VACCINES

Selection of vaccines by individual countries should be made after consideration of international recommendations, epidemiology, and national priorities. All vaccines should comply with WHO recommendations for the production, control, and evaluation of vaccines and other biological substances

Vaccines may consist of a live attenuated or inactivated form of a virus or bacteria, or an extract of or detoxified exotoxin produced by a microorganism. Some inactivated vaccines are adsorbed onto an adjuvant to enhance the antibody response.

Adverse effects

Vaccines are generally both effective and safe. 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. However, the systemic symptoms that may arise with the measles or the measles, mumps, and rubella (MMR) vaccine occur 5–12 days after vaccination. Serious reactions are rare, but hypersensitivity reactions including anaphylaxis (see Section 3) have been reported. If a serious adverse event occurs (such as severe allergy or anaphylaxis) following a dose of any 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. Vaccines are contraindicated in individuals with known severe hypersensitivity to any component; consult the manufacturer's literature for the specific composition of individual vaccines.

HIV infection

The likelihood of successful immunization is reduced in some HIV-infected individuals, but the risk of serious adverse effects remains low, except for BCG. Specific precautions and contraindications in HIV infection are given in the listings for the individual vaccines.

Live vaccines

When 2 live virus vaccines are required (and are not available as a combined preparation) they should be given either simultaneously at different sites or with an interval of at least 4 weeks.

Live vaccines should not be routinely administered to pregnant women because of the possible harm to the fetus but where there is significant risk of exposure, the need for immunization may outweigh any possible risk to the fetus.

Postimmunization fever

If fever develops after childhood immunization, the infant can be given a dose of paracetamol (60 mg), followed if necessary by a second dose 4–6 hours later. If fever persists after the second dose, medical advice should be sought (see *also* Section 2.1).

Fever from any cause, including immunization, increases risk of febrile convulsions when there is a personal or family history of febrile convulsions. When immunization of these children is recommended, advice on prevention of fever should be given before administration of the vaccine.

- **BCG vaccine**

Tuberculosis (TB) is a bacterial infection caused by *Mycobacterium tuberculosis*, transmitted from person to person through respiratory contact.

WHO recommends that all infants in highly endemic countries receive a single dose of BCG vaccine as soon as possible after birth.

Infants exposed to smear-positive pulmonary tuberculosis shortly after birth should not receive BCG vaccination until completion of 6 months of prophylactic isoniazid treatment (see Section 6.2.4).

- **Dosage form**

- Injection: Powder containing live bacteria of a strain derived from BCG

- **Use**
 - Active immunization against tuberculosis
- **Contraindications**
 - See introductory notes.
 - Also HIV infection, immunodeficiency, patients receiving immunosuppressive therapy
 - Generalized septic skin conditions
- **Precautions**
 - Pregnancy: Appendix B
 - Eczema, scabies (vaccine site must be lesion-free)
 - ***Interactions:*** Appendix A
- **Dose**

Immunization against tuberculosis, by intradermal injection

 - **INFANT** up to 12 months: 0.05 ml
- **Reconstitution and administration**
 - According to manufacturer's directions
- **Adverse effects**
 - Rarely lymphadenitis, local ulceration, disseminated BCG infection in immunodeficient individuals (5 cases in 1 million doses), and osteitis

Type of vaccine	Live attenuated vaccine
Number of doses	1 dose
Time of administration	As soon as possible after birth
Booster dose	No
Contraindication	HIV infection
Adverse reactions	Abcess at injection site, lymphadenitis and disseminated infection of BCG
Special measures	Injection <i>by intradermal</i> route using disposable syringe
Administering dose	0.05 ml
Injection site	Left arm
Injection method	Intradermal
Temperature	Between 2° and 8° Celsius, and never to be frozen

- **DPT-HepB +Hib composite vaccine**

DPT-HepB+Hib vaccine is a type of composite vaccine called pentavalent, because it produces immunity against five diseases: hepatitis B (HepB), diphtheria-pertussis-tetanus (DPT) and hemophilus influenza type b (Hib).

Possible potential reactions: This vaccine should **NEVER** be administered to newborns during birth. Severe reactions of DPT-HepB+Hib are the same as for DPT. In case of such severe reactions, the health worker is responsible to report the issue to their immediate supervisor. If a child develops such reactions during the first dose, a second dose should **NOT** be given.

Warning

The DPT-HepB+Hib vaccine should **NEVER** be administered to newborns during birth.

Common side effects include pain, local sensitivity, redness, and swelling in the injection area in some children, which disappears after 1–3 days. Some children develop moderate fever due to receiving vaccine.

Type of vaccine	Pentavalent composite vaccine
Number of doses	3 principal doses
Time of administration	6, 10, and 14 weeks old
Booster dose	No
Contraindication	During birth
Adverse reactions	Ordinary local reactions
Special measures	Should not be administered during birth and after 6 years old
Administering dose	0.5 ml
Time between doses	At least 4 weeks
Injection site	In the middle third of the thigh
Injection method	Intramuscular with 90° angle
Temperature	Between 2° and 8° Celsius, and never to be frozen

- **Hepatitis B vaccine**

Hepatitis B is caused by the hepatitis B virus. It is transmitted in blood and blood products, by sexual contact, and by contact with infectious body fluids. Persons at increased risk of infection because of their lifestyle, occupation, or other factors, include parenteral drug abusers, individuals

who change sexual partners frequently, staff and inmates of custodial institutions, health care workers who are at risk of injury from blood-stained sharp instruments, dialysis patients, and hemophiliacs. Also at risk are babies born to mothers who are HbsAg-positive (hepatitis B virus surface antigen–positive), those having medical or dental procedures in countries with high prevalence, and travelers to endemic countries.

WHO recommends that hepatitis B vaccine be given as part of the national infant immunization program. Catch-up immunization should be considered for older age groups and high-risk individuals who have not been previously immunized, in countries with intermediate or low hepatitis B endemicity.

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 either a monovalent or a fixed-combination preparation with other antigens such as *Hemophilus influenzae* type b, poliomyelitis, and diphtheria-pertussis-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 3- or 4-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 the DPT vaccine or other vaccines.

A reduced immunogenicity of the vaccine may occur in individuals with immunodeficiency, including those advanced HIV infection, diabetes, chronic liver disease, or chronic renal failure.

- **Hepatitis B (HepB) purified antigen vaccine**

- **Dosage form**

- Injection: Single dose in 1 ml ampoule

- **Uses**

- Active immunization against hepatitis B

- **Contraindications**

- See introductory notes.

- **Precautions**

- See introductory notes.
- Also diabetes mellitus
- Chronic renal failure: Appendix D
- Chronic liver disease: Appendix E (reduced immunogenicity)

- **Dose**

Primary immunization of children against hepatitis B (3-dose schedule), by intramuscular injection

- **CHILD:** 1 dose of 0.5 ml given between 6 weeks and 15 years of age, followed by 2 doses, each of 0.5 ml given at intervals of 4 weeks; alternatively, 1 dose of 0.5 ml at birth, followed by 2 doses, each of 0.5 ml, given at 6 and 14 weeks of age

Primary immunization of children against hepatitis B (4-dose schedule), by intramuscular injection

- **CHILD:** 1 dose of 0.5 ml at birth, followed by 3 doses, each of 0.5 ml, at 6, 10, and 14 weeks of age

Note: Immunization with hepatitis B vaccine can be timed to correlate with the DPT schedule.

Immunization of unimmunized high-risk persons against hepatitis B, by intramuscular injection

- **ADULT** and **CHILD** over 15 years of age: 3 doses, each 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
- **CHILD** under 15 years: 0.5 ml

Note: 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.
- The anterolateral thigh is the preferred site in infants and young children.
- It should not be injected into the buttock (vaccine efficacy reduced).

- **Adverse effects**

- See introductory notes.

- **Oral polio vaccine (OPV)**

Oral polio vaccine protects body against polio virus, which causes paralysis. This vaccine is available in monovalent, bivalent, and trivalent forms.

This vaccine is prepared in following two forms:

1. Plastic bottles with dropper integrated or attached

2. Glass bottles with separate droppers

Possible potential adverse reactions and side effects: Generally, OPV vaccine does not cause any potential adverse reaction. But in every 1 million administered doses, 2–4 cases of vaccine-associated paralytic polio (VAPP) develop after and due to administration of vaccine.

Type of vaccine	OPV vaccine derived from live attenuated virus
Number of doses	5 doses
Time of administration	During birth,† 6 weeks, 10 weeks, 14 weeks, and 9 months old
Booster dose†	Supplementary dose is administered during national vaccine days for polio eradication.
Contraindication	No contraindication
Adverse reactions	2–4 rare cases of vaccine-associated paralytic polio in every 1 million doses after administration of vaccine
Special measures	Give injectable polio vaccine to children with impaired immune system.
Administering dose	2 drops
Route of administration	Orally
Administration method	Orally with 45° angle
Temperature	Between 2° and 8° Celsius

† OPV is administered during birth in polio-endemic countries.

- **Measles vaccine**

Measles is an acute viral infection transmitted by close respiratory contact. Immunization against measles is recommended for all infants and young children, and also for adolescents and adults who are susceptible or at high risk of exposure.

The measles vaccine is a live attenuated vaccine, available either as a single-antigen vaccine or combined with either rubella (MR) or mumps and rubella (MMR) vaccines; the combined vaccines are usually given as part of the primary immunization schedule. No evidence has been found for the alleged associations between measles or MMR immunization and serious developmental disorders such as autism, or chronic bowel disease.

- **Dosage form**

- Powder for injection, live attenuated measles virus (10 doses per vial)

- **Uses**

- Active immunization against measles

- **Precautions**

- Pregnancy: Appendix B
- **Interactions:** Appendix A

- **Dose**

Primary immunization of children against measles

- See below table.

Immunization of HIV-infected infants against measles (unless severely immunocompromised), by intramuscular or subcutaneous injection

- **INFANT:** 1 dose of 0.5 ml at 6 months of age, followed by a second dose of 0.5 ml at 9 months of age

Prophylaxis in susceptible individuals after exposure to measles, by intramuscular or subcutaneous injection within 48 hours of contact

- **ADULT and CHILD** over 9 months: 1 dose of 0.5 ml
- **Reconstitution and administration**
 - According to manufacturer's directions
 - **Adverse effects**
 - Malaise, fever, also local lymphadenopathy, rash
 - Rarely thrombocytopenia purpura

Type of vaccine	Measles vaccine
Number of doses	2 doses
Time of administration	During 9th month and 18th months of age
Booster dose	Supplementary dose is administered during national vaccine days.
Contraindications	Hypersensitivity to primary dose, pregnancy, congenital disorders, and immunodepressions
Adverse reactions	See above.
Special measures	None
Administering dose	1 dose of 0.5 ml
Injection site	Arm
Injection method	Subcutaneous at 45° angle
Temperature	Between 2° and 8° Celsius

- **Pneumococcal conjugated vaccine / 7- and 23-valent**

Streptococcus pneumoniae causes serious infections 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. The 7-valent conjugate vaccine (PCV-7) provides effective protection in young children; the primary schedule usually consists of 3 doses, administered at intervals of at least 4 weeks. 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 who have not been previously vaccinated and to children aged 2–5 years 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, and therefore is not recommended for use in this age group.

- **Dosage form**

- Injection: 1 dose per vial

- **Uses**

- Active immunization against *Streptococcus pneumoniae*

- **Contraindication**

- If a patient develops anaphylactic reactions to the first dose, the second dose should be avoided.

- **Dose**

Primary immunization against infection by Streptococcus pneumoniae (PCV-7), by intramuscular injection

- **INFANT:** 3 doses, each of 0.5 ml, at 6, 10, and 14 weeks of age; alternatively, 3 doses, each of 0.5 ml, at 2, 4, and 6 months of age; a reinforcing dose of 0.5 ml can be given at 12–15 months of age.
- **CHILD** 1–5 years: 0.5 ml as a single dose

- **Administration**

- The vaccine should be given in the deltoid region in young children; the anterolateral thigh is the preferred site in infants.

- **Adverse effects**

- Adverse effects of the vaccine are mild and occur in 50% of children; they include insomnia, anorexia, and redness at injection site.

- **Rotavirus vaccine**

Rotaviruses are the most common cause of severe diarrhea in infants and young children. The virus is transmitted via the fecal-oral route from person to person in close contact or via contaminated fomites.

Two live oral attenuated rotavirus vaccines are currently available (the monovalent and the pentavalent); both are effective against severe rotavirus infection. Rotavirus vaccine is administered orally in a 2- or 3-dose schedule, starting at between 6 and 12 weeks of age, with an interval of at least 4 weeks between doses. The 2-dose schedule should be completed before 24 weeks of age (preferably before 16 weeks).

The 3-dose schedule is usually given at ages 2, 4, and 6 months; all 3 doses should be completed before 32 weeks of age. Subsequent booster doses after the primary schedule are not recommended.

- **Dosage form**
 - Oral suspension, live attenuated rotavirus
- **Use**
 - Active immunization against rotavirus infection
- **Contraindications**
 - Immunodeficiency
 - History or predisposition to intussusception
- **Precaution**
 - Postpone administration in infants with acute gastroenteritis or serious febrile illness
- **Dose**

Immunization of infants against rotavirus infection, by mouth

- **INFANT** 6–12 weeks of age: 2–3 doses separated by at least 4 weeks
-
- **Adverse effects**
 - Mild and transient gastrointestinal symptoms
-
- **Rubella vaccine**

Rubella is normally a mild childhood disease; it is transmitted from person to person via the respiratory route. The primary purpose of rubella

vaccination is to prevent rubella infection during pregnancy, which can lead to fetal death and congenital rubella syndrome (characterized by multiple birth defects including mental retardation, and hearing and visual impairment).

Rubella vaccine should be given to women of childbearing age if they are seronegative to protect them from the risks of rubella in pregnancy.

Rubella vaccine should **NOT** be given in pregnancy and patients should be advised not to become pregnant within 1 month of vaccination.

However, congenital rubella syndrome has not been reported following inadvertent immunization shortly before or during pregnancy. There is no evidence that the vaccine is teratogenic and termination of pregnancy following inadvertent immunization should not be recommended. There is no risk to a pregnant woman from contact with recently vaccinated persons, as the vaccine virus is not transmitted.

A number of rubella vaccines are available, either as single-antigen vaccines or combined with measles and mumps vaccines (MMR), or the measles vaccine (MR).

- **Dosage form**

- Powder for injection, live attenuated rubella virus

- **Uses**

- Active immunization against rubella

- **Contraindications**

- Untreated active tuberculosis
- Pregnancy: Appendix B
- **Interactions:** Appendix A

- **Dose**

Immunization against rubella, by subcutaneous injection

- **ADULT** and **CHILD**: 0.5 ml as a single dose

- **Reconstitution and administration**

- According to manufacturer's directions

- **Adverse effects**

- Rash, lymphadenopathy, paresthesia
- Transient arthralgia and arthritis in unimmunized adolescent and adult females
- Rarely thrombocytopenia

- **Tetanus vaccine**

Tetanus is caused by the action of a neurotoxin of *Clostridium tetani* in necrosed tissues such as occur in dirty wounds. Tetanus vaccines are based on tetanus toxoid, which is adsorbed on aluminium or calcium salts to increase immunogenicity. Tetanus toxoid is available both as single antigen and in vaccine combinations. WHO recommends a childhood tetanus immunization schedule of 5 doses: The primary series of 3 doses should be given during the first year of life as the combined diphtheria-pertussis-tetanus (DPT). The 4th booster dose with a tetanus toxoid-containing vaccine should be given at 4–7 years and the 5th dose during adolescence at 12–15 years. A sixth dose can be given in early adulthood for life-long protection. When tetanus prophylaxis is needed following injury, combined diphtheria and tetanus preparations should be used rather than tetanus alone to promote immunity against diphtheria. Neonatal tetanus due to infection of the baby's umbilical stump during unclean delivery is the cause of many deaths of newborn infants. Control of neonatal tetanus may be achieved by ensuring adequate hygiene

during delivery and by ensuring protective immunity of mothers in late pregnancy. Alternatively, women of childbearing age may be immunized against tetanus with a single-antigen vaccine.

- **Dosage form**

- Injection: 20 doses per vial

- **Uses**

- Active immunization against tetanus and neonatal tetanus; tetanus prophylaxis as part of wound management (tetanus-prone wounds and clean wounds)

Antitetanus immunoglobulin: If the schedule requires tetanus vaccine and antitetanus immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites.

- **Dose**

Primary immunization of unimmunized adolescents and adults (including women of childbearing age) against tetanus, by intramuscular injection

- **ADULT and ADOLESCENT:** 3 doses, each of 0.5 ml, with an interval of not less than 4 weeks between the first and second doses and 6 months between the second and third doses; followed by 2 reinforcing doses, each of 0.5 ml, the first at least 1 year after completion of the primary course and the second dose at least 1 year later

Reinforcing immunization of adults against tetanus, by intramuscular injection

- **ADULT:** 2 doses, each of 0.5 ml, the first 10 years after completion of the primary course, and the second dose 10 years later

Immunization of unimmunized pregnant women against tetanus, by intramuscular injection

- **ADULT:** 2 doses, each of 0.5 ml, with an interval of at least 4 weeks between each dose (second dose at least 2 weeks before delivery), followed by a third dose of 0.5 ml 6 months later; and 2 booster doses, each of 0.5 ml, the first at least 1 year after completion of the primary course and the second dose at least 1 year later

Management of tetanus-prone wounds and clean wounds, by intramuscular injection

- **ADULT:** 0.5 ml as a single dose (dose schedule dependent on the immune status of the patient and the level of contamination of the wound)

- **Adverse effects**

- Rarely skin erythema and fever

SECTION 20: Muscle relaxants (peripherally acting) and cholinesterase inhibitors

MUSCLE RELAXANTS

Muscle relaxants used in surgery are classified according to their mode of action as either depolarizing or non-depolarizing neuromuscular-blocking drugs. Their use allows abdominal surgery to be carried out under light anesthesia. They should never be given until it is certain that general anesthesia has been established, and ventilation must be mechanically assisted until they have been completely inactivated.

Suxamethonium is the only widely used depolarizing muscle relaxant. It produces rapid, complete paralysis, which is very short-lasting in most patients and is of particular value for laryngoscopy and intubation. Should paralysis be prolonged, ventilation must be assisted until muscle function is fully restored. Suxamethonium normally produces a phase I (depolarizing) neuromuscular block. After high doses or prolonged use, the nature of the block changes to a phase II (non-depolarizing) block; this phase II block (also known as a dual block) is associated with prolonged neuromuscular blockade and apnea.

Cholinesterase inhibitors

Reversal of block

Cholinesterase inhibitors, such as **neostigmine**, are used at the end of an operation to reverse the muscle paralysis produced by non-depolarizing blocking drugs, such as vecuronium. Neostigmine must not be used with depolarizing blocking drugs, such as suxamethonium, since neostigmine will prolong the muscle paralysis. Neostigmine is also used to treat postoperative non-obstructive urinary retention.

Myasthenia gravis

Cholinesterase inhibitors, such as **neostigmine** and **pyridostigmine**, are used in the symptomatic treatment of myasthenia gravis. They act by inhibiting acetylcholinesterase, thereby prolonging the action of acetylcholine, and thus enhancing neuromuscular transmission; this produces at least a partial improvement in most myasthenic patients but complete restoration of muscle strength is rare. Unless the patient has difficulty in swallowing, cholinesterase inhibitors are given by mouth. Pyridostigmine has a slower onset (usually within 30–60 minutes), but a longer duration of effect than neostigmine; it also tends to cause fewer muscarinic effects such as diarrhea, abdominal cramps, and excess salivation, and therefore is usually preferred. Doses should be carefully adjusted to avoid precipitating a cholinergic crisis due to overdosage; this must be differentiated from a myasthenic crisis caused by disease progression and consequent underdosage; the principal effect in both cases is increased muscle weakness.

In myasthenic crisis, if the patient has difficulty in breathing and in swallowing, the cholinesterase inhibitor must be given by intramuscular or subcutaneous injection; neostigmine is usually preferred over pyridostigmine in such cases. To reduce the muscarinic effects of neostigmine, atropine (Section 1.3) should also be given.

A corticosteroid, such as prednisolone (Section 18.1), is also used for the treatment of myasthenia gravis; addition of the immunosuppressant azathioprine may allow a dose reduction of both the corticosteroid and of the anticholinesterase.

- **Neostigmine**

- **Dosage form**

- Tablet: 15 mg (bromide)
 - Injection solution: 0.5 mg/ml (methylsulfate) in 10 ml ampoule

- **Uses**

- Myasthenia gravis
- Reversal of non-depolarizing muscle relaxants administered during surgery, postoperative non-obstructive urinary retention

- **Contraindications**

- Recent intestinal or bladder surgery
- Mechanical intestinal or urinary tract obstruction
- After suxamethonium
- Pneumonia
- Peritonitis

- **Precautions**

- Asthma
- Urinary tract infections
- Cardiovascular disease including arrhythmias (especially bradycardia, vagotonia, recent myocardial infarction, or atrioventricular block)
- Hyperthyroidism
- Hypotension
- Peptic ulcer
- Epilepsy
- Parkinsonism
- Renal impairment: Appendix D
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Interactions:** Appendix A

- **Dose**

Myasthenia gravis, by mouth as neostigmine bromide

- **ADULT:** Initially 15–30 mg at suitable intervals throughout the day (usual duration of action 2–4 hours), gradually increased until desired response is obtained; usual total daily dose within range, 75–300 mg, given at appropriate intervals when high doses are required (doses above 180 mg daily are not usually well tolerated)
- **NEONATE:** Initially 1–2 mg every 4 hours, 30 minutes before feeds
- **CHILD** up to 6 years: Initially 7.5 mg
- **CHILD** 6–12 years: Initially 15 mg; usual total daily dose, 15–90 mg given in divided doses at appropriate intervals

Myasthenia gravis, by subcutaneous or intramuscular injection

- **ADULT:** 1–2.5 mg as required; usual total daily dose 5–20 mg
- **NEONATE:** 50–250 micrograms every 4 hours, 30 minutes before feeds (not usually required beyond 8 weeks of age)
- **CHILD:** 200–500 micrograms as required

Reversal of non-depolarizing block, by intravenous injection over 1 minute

- **ADULT:** 2.5 mg, followed if necessary by supplements of 500 micrograms to maximum total dose of 5 mg
- **CHILD:** 40 micrograms/kg (titrated using peripheral nerve stimulator)

Note: To reduce muscarinic effects, administer atropine sulfate by intravenous injection (**ADULT:** 0.6–1.2 mg, **CHILD:** 20 micrograms/kg) with or before neostigmine

Postoperative urinary retention, by subcutaneous or intramuscular injection

- **ADULT:** 500 micrograms (catheterization required if urine not passed within 1 hour)

- **Adverse effects**

- Increased salivation, nausea and vomiting, abdominal cramps, diarrhea
- Signs of overdose include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus, bradycardia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, and weakness eventually leading to fasciculation and paralysis
- Thrombophlebitis reported
- Rash-associated tablet (bromide salt) formulations

- **Suxamethonium**

- **Dosage form**

- Injection: 50 mg powder (chloride)/ml in 2 ml ampoule

Note: Powder formulation is usually preferred; liquid requires refrigerated storage.

- **Uses**

- Brief muscular paralysis during endotracheal intubation, endoscopy, and electroconvulsive therapy

- **Contraindications**

- Inability to maintain clear airway
- Personal or family history of malignant hyperthermia

- Neurological disease involving acute wasting of major muscle, prolonged immobilization (risk of hyperkalemia)
- Personal or family history of congenital myotonic disease
- Duchenne muscular dystrophy
- Myasthenia gravis
- Glaucoma, ocular surgery
- Liver disease
- Burns
- Low plasma cholinesterase activity (including severe liver disease)
- Hyperkalemia

○ **Precautions**

- Digitalis toxicity or recent digitalization
- Cardiac, respiratory, or neuromuscular disease
- Paraplegia, spinal cord injury, or severe trauma
- Severe sepsis (risk of hyperkalemia)
- Prolonged apnea on repeated injection (infusion preferred for long surgical procedures)
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Children
- **Interactions:** Appendix A

○ **Dose**

Muscle relaxation, by intramuscular injection

- **INFANT:** Up to 4–5 mg/kg
- **CHILD:** Up to 4 mg/kg; maximum 150 mg

Muscle relaxation, by intravenous injection

- **ADULT** and **CHILD**: 1 mg/kg, followed if necessary by supplements of 0.5–1 mg/kg at 5–10 minute intervals
- **INFANT**: 2 mg/kg

Muscle relaxation (prolonged procedures), by intravenous infusion

- **ADULT**: 2.5–4 mg/min of solution containing 1–2 mg/ml; maximum 500 mg/hour
- **CHILD**: Reduce infusion rate according to body weight, but a total dose of 150 mg should not be exceeded

○ **Adverse effects**

- Postoperative muscle pain, particularly in female patients ambulant after operation
- Myoglobinuria; myoglobinemia; prolonged apnea
- Increased intraocular pressure
- Hyperkalemia
- Bradycardia, hypotension, and arrhythmias, particularly with halothane (but with repeated doses, tachycardia, hypertension)
- Increased salivary, bronchial and gastric secretions
- Transient rise in intragastric pressure
- Hypersensitivity reactions including flushing, rash, urticaria, bronchospasm, and shock (more common in women, in history of allergy, or in asthmatics)
- Rarely malignant hyperthermia (but often fatal)

SECTION 21: Ophthalmological preparations

ADMINISTRATION OF EYE PREPARATIONS

Preparations for use in the eye should be sterile when issued. Use of single-application containers is preferable; multiple-application preparations include antimicrobial preservatives and when used particular care should be taken to prevent contamination of the contents, for example, by avoiding contact between the applicator and the eye or other surfaces.

Eyedrops are generally instilled into the lower conjunctival sac, which is accessed by gently pulling down the lower eyelid to form a pocket into which one drop is instilled. The eye should be kept closed for as long as possible after application, preferably 1–2 minutes. A small amount of eye ointment is applied similarly; the ointment melts rapidly and blinking helps to spread it.

When two different eyedrops are required at the same time, dilution and overflow may occur if one immediately follows the other; an interval of at least 5 minutes should therefore be allowed between the two applications.

Systemic absorption, which may occur after topical application of eyedrops, can be minimized by using the finger to compress the lacrimal sac at the medial canthus for at least 1 minute after instillation of the drops. This helps block the passage of the drops through the naso-lacrimal duct.

Performance of skilled tasks

Application of eye preparations may cause blurring of vision, which is generally transient; patients should be advised not to carry out skilled tasks, such as operating machinery or driving, until their vision has cleared.

21.1. ANTI-INFECTIVE AGENTS

Blepharitis, conjunctivitis, keratitis, and endophthalmitis are common acute infections of the eye, all of which can be treated topically. However, in some cases, for example, in gonococcal conjunctivitis, both topical and systemic anti-infective treatment may be necessary. Blepharitis and conjunctivitis are often caused by *Staphylococcus*, while keratitis and endophthalmitis may be bacterial, viral, or fungal. Bacterial blepharitis is treated with an antibacterial eye ointment or drops. Although most cases of acute bacterial conjunctivitis may resolve spontaneously, anti-infective treatment shortens the infectious process and prevents complications. Acute infective conjunctivitis is treated with antibacterial eyedrops by day and eye ointment applied at night. A poor response may indicate viral or allergic conjunctivitis. Keratitis requires immediate specialist treatment.

Aciclovir is an antiviral used in the treatment of keratitis due to herpes simplex virus. Lesions usually heal after 5–9 days of treatment. For systemic treatment of keratitis with antivirals, see Section 6.4.1.

Gentamicin is a broad-spectrum bactericidal aminoglycoside antibiotic with particular activity against *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, and other bacteria that may be implicated in blepharitis or conjunctivitis. Topical application may lead to systemic absorption and possible adverse effects.

Tetracycline is a broad spectrum antibiotic with activity against many gram-positive and gram-negative bacteria, including *N. gonorrhoeae*, and most chlamydia, rickettsia, mycoplasma and spirochetes. Ophthalmic tetracycline is used in blepharitis, conjunctivitis, and keratitis produced by susceptible bacteria. Tetracycline is also used in the treatment of trachoma caused by *Chlamydia trachomatis* and in the prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) caused by *N. gonorrhoeae* and *C. trachomatis*.

- **Aciclovir**

- **Dosage form**

- Eye ointment: 3%

- **Use**

- Keratitis caused by herpes simplex

- **Administration**

Herpes simplex keratitis, applied directly to the eye

- **ADULT** and **CHILD**: 1 cm of ointment 5 times daily

Note: Continue for at least 3 days after healing is complete.

- **Adverse effects**

- Local irritation including transient mild stinging, inflammation
 - Superficial punctuate keratopathy reported
 - Very rarely hypersensitivity reactions including angioedema

- **Chloramphenicol**

- **Dosage form**

- Eye ointment: 1%
 - Eyedrops: 0.5%

- **Use**

- Chloramphenicol has a broad spectrum of activity and is a drug of choice in the local treatment of eye infections

Note: It is well tolerated, and the evidence of relation with aplastic anemia is very weak.

- **Administration**

For various infections, applied directly to the eye

- Ointment is used once during nighttime when eyedrop is used daily; otherwise if eyedrop is used alone 3–4 times daily.
- Eyedrop initially every 2 hours, then according to response the interval is reduced
- Treatment should be continued until 48 hours after complete recovery.

- **Adverse effect**

- Transient feeling of stinging

- **Gentamicin**

Gentamicin is a representative ophthalmic antibacterial. Various medicines can serve as alternatives.

- **Dosage form**

- Eyedrops: 0.3% (sulfate) in 5 ml bottle
- Eye ointment: 3 mg/g (sulfate) in 3.5 g tube

- **Uses**

- Blepharitis
- Bacterial conjunctivitis

- **Contraindication**

- Hypersensitivity to aminoglycoside group of antibiotics

- **Precautions**

- Prolonged use may lead to skin sensitization and emergence of resistant organisms, including fungi.
- Discontinue if there is purulent discharge, inflammation or exacerbation of pain.

- **Administration**

Mild-to-moderate infection, by ocular instillation

- **ADULT** and **CHILD**: 1 drop every 2 hours, reducing frequency as infection is controlled, then continue for 48 hours after healing is complete

Severe infection, by ocular instillation

- **ADULT** and **CHILD**: 1 drop every hour, reducing frequency as infection is controlled, then continue for 48 hours after healing is complete

- **Adverse effects**

- Burning, stinging, itching, dermatitis

- **Ciprofloxacin**

- **Dosage form**

- Eyedrops: 0.3% in 2.5 ml bottle.

- **Uses**

- Eye infections and corneal ulcer
- Repeated administration is necessary in the 2 first days of corneal ulcer

- **Contraindications**
 - Child under 1 year of age
 - Pregnancy
 - Breast-feeding
- **Administration**

Corneal ulcer, by ocular instillation

 - **ADULT and CHILD:** 1–2 drops every 15 minutes for 6 hours in the first day, then every 30 minutes; on the second day every 1 hour; on the third and fourth days every 4 hours; for maximum of 21 days
- **Adverse effects**
 - Unpleasant taste in the mouth immediately after instilling the drop, redness, burning, numbness, itching, or discomfort of the eye, or the sensation that something is in the eye
 - The eye can also appear tired, stained, or swollen.
- **Sulfacetamide**
 - **Dosage form**
 - Eyedrops: 10%, 20%, and 30%* in 15 ml bottle
 - **Uses and administration**
 - Sulfacetamide is a sulfonamide antibacterial that is applied, as the sodium salt, in infections or injuries of the eyes, although it is rarely of much value.
 - **Adverse effects**
 - Local application of sulfacetamide sodium to the eye may cause burning or stinging but this is rarely severe enough to require stopping treatment.

- For precaution, interactions and contraindication, see Sulfonamides.

- **Tetracycline**

Tetracycline is a representative ophthalmic antibacterial. Various medicines can serve as alternatives.

- **Dosage form**

- Eye ointment: 1% in 5 g tube (hydrochloride)

- **Uses**

- Superficial bacterial infection of the eye; mass treatment of trachoma in endemic areas
- Prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis*

- **Contraindication**

- Hypersensitivity to tetracycline group of antibiotics

- **Precautions**

- Prolonged use may lead to overgrowth of non-susceptible organisms.

- **Administration**

Superficial bacterial infection, applied directly to the eye

- **ADULT** and **CHILD** aged over 8 years: 1 application of ointment 3–4 times daily

Prophylaxis of neonatal conjunctivitis, applied directly to the eye

- **NEONATE:** At birth after cleansing eyes with sterile gauze, 1 application of ointment into each eye; close eyelids and massage gently to aid spread of ointment

Trachoma, intermittent treatment, applied directly to the eye

- **ADULT and 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, applied directly to the eye

- **ADULT and CHILD:** 1 application of ointment into each eye twice daily for at least 6 weeks

- **Adverse effects**

- Rash
- Rarely stinging and burning

21.2. ANTI-INFLAMMATORY AGENTS

Ophthalmic corticosteroids should only be used under supervision of an ophthalmologist, as inappropriate use is potentially blinding. Dangers include the development of open-angle glaucoma (chronic simple glaucoma) and cataracts, and the aggravation of simple herpes simplex epithelial lesions into extensive corneal ulcers and subsequent permanent corneal scarring, with possible damage to vision and even loss of the eye.

Corticosteroids such as prednisolone are useful in the treatment of inflammatory eye conditions, including uveitis and scleritis. They are also used for reducing postoperative ocular inflammation. Before administration of an ophthalmic corticosteroid, the possibility of bacterial, viral, or fungal infection should be excluded. Treatment should be with the lowest effective dose for the shortest

possible time; if long-term therapy (more than 6 weeks) is unavoidable, withdrawal of an ophthalmic corticosteroid should be gradual to avoid relapse.

- **Prednisolone**

Prednisolone is a representative ophthalmic corticosteroid. Various drugs can serve as alternatives.

- **Dosage form**

- Ophthalmic drops: 0.5% and 1% (sodium phosphate)

- **Uses**

- Short-term local treatment of inflammation of the eye

- **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

Note: Use only under the supervision of an ophthalmologist.

- **Administration**

Inflammation of the eye, by ocular instillation

- **ADULT** and **CHILD:** 1 drop every 1–2 hours, reducing frequency as inflammation is controlled

- **Adverse effects**

- Secondary ocular infection
- Impaired corneal healing (due to corneal thinning), optic nerve damage, cataract
- Glaucoma, mydriasis, ptosis, epithelial punctate keratitis, delayed hypersensitivity reactions including burning and stinging

21.3 LOCAL ANESTHETICS

Topical local anesthetics are employed for simple ophthalmological procedures and for short operative procedures involving the cornea and conjunctiva.

Tetracaine, available in a 0.5% ophthalmic solution, provides a rapid local anesthesia that lasts for 15 minutes or more. Prolonged or unsupervised use of tetracaine is not recommended.

- **Tetracaine**

Also known as *amethocaine*

Tetracaine is a representative ophthalmic local anesthetic. Various drugs can serve as alternatives.

- **Dosage form**

- Ophthalmic drops: 0.5% in 15 ml bottle (hydrochloride)

- **Uses**

- Short-acting local anesthesia of the cornea and conjunctiva

- **Contraindications**

- Hypersensitivity to ester-type local anesthetics
- Eye inflammation or infection

- **Precautions**

- Avoid prolonged use (risk of severe keratitis, permanent corneal opacification, scarring, and delayed corneal healing).
- Protect eye from dust and bacterial contamination until sensation is fully restored.

- **Administration**

Local anesthesia, by ocular instillation

- **ADULT** and **CHILD**: 1 drop

- **Adverse effects**

- Burning, stinging, redness
- Rarely allergic reactions may occur

21.4 MIOTICS AND ANTIGLAUCOMA MEDICINES

Glaucoma is normally associated with raised intraocular pressure and eventual damage to the optic nerve, which may result in blindness. The rise in pressure is almost always due to reduced outflow of aqueous humor, the inflow remaining constant. The most common condition is chronic open-angle glaucoma (chronic simple glaucoma), in which the intraocular pressure increases gradually and the condition is usually asymptomatic until well advanced. In contrast, angle-closure glaucoma (closed-angle glaucoma) usually occurs as an acute emergency resulting from a rapid rise in intraocular pressure; if treatment is delayed, chronic angle-closure glaucoma may develop. In ocular hypertension, intraocular pressure is raised without signs of optic nerve damage.

Drugs used in the treatment of glaucoma lower the intraocular pressure by a variety of mechanisms, including reducing the secretion of aqueous humor by the ciliary body, or increasing the outflow of the aqueous humor by the opening of the trabecular network. Antiglaucoma drugs used include a beta-blocker (beta-adrenoceptor antagonist), a miotic, or a sympathomimetic such as epinephrine

(Section 21.5); systemic administration of a carbonic anhydrase inhibitor may be used as an adjunct.

Timolol is a non-selective beta-blocker that reduces the secretion of aqueous humor. A beta-blocker, applied topically, is usually the drug of choice for both initial and maintenance treatment of chronic open-angle glaucoma. If further reduction in intraocular pressure is required, a miotic, a sympathomimetic, or a systemic carbonic anhydrase inhibitor may be used together with timolol. In angle-closure glaucoma, however timolol should always be used with a miotic, not alone. Since systemic absorption can occur, an ophthalmic beta-blocker should not be used in patients with asthma or a history of obstructive pulmonary disease, unless no alternative is available; in such cases precautions should be taken to guard against bronchospasm.

A miotic such as **pilocarpine**, through its parasympathomimetic action, contracts the iris sphincter muscle and the ciliary muscle, and opens the trabecular network. It is used in chronic open-angle glaucoma either alone or, if required, with a beta-blocker, epinephrine, or a systemic carbonic anhydrase inhibitor. Pilocarpine is used with systemic **acetazolamide** in an acute attack of angle-closure glaucoma prior to surgery; however, it is not advisable to use pilocarpine after surgery because of a risk of posterior synechiae forming. Systemic absorption of topically applied pilocarpine can occur, producing muscarinic adverse effects.

Acetazolamide, by reducing carbonic anhydrase in the eye, reduces the production of aqueous humor and so reduces intraocular pressure. It is used systemically as an adjunct in chronic open-angle glaucoma unresponsive to treatment with topically applied antiglaucoma drugs. Prolonged therapy with acetazolamide is not normally recommended, but if treatment is unavoidable blood counts and plasma electrolyte concentrations should be monitored. Acetazolamide is also used as part of emergency treatment for an acute attack

of angle-closure glaucoma; however, it should not be used in chronic angle-closure glaucoma as it may mask deterioration of the condition.

- **Acetazolamide**

- **Dosage form**

- Tablet: 250 mg

- **Uses**

- As an adjunct in the treatment of chronic open-angle glaucoma
 - Secondary glaucoma
 - As part of preoperative treatment of acute angle-closure glaucoma

- **Contraindications**

- Hypersensitivity to sulfonamides
 - Chronic angle-closure glaucoma (may mask deterioration)
 - Hypokalemia, hyponatremia, hyperchloremic acidosis
 - Renal impairment: Appendix D
 - Severe hepatic impairment: Appendix E

- **Precautions**

- Elderly
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Diabetes mellitus
 - Pulmonary obstruction
 - Monitor blood count and electrolytes if used for long periods
 - **Interactions:** Appendix A

- **Skilled tasks:** May impair ability to perform skilled tasks (for example, operating machinery or driving)

- **Dose**

Chronic open-angle glaucoma, secondary glaucoma, by mouth

- **ADULT:** 0.25– 1 g daily in divided doses

- **Adverse effects**

- Nausea, vomiting, diarrhea, taste disturbances
- Loss of appetite, paresthesia, 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, melena, glycosuria, hematuria, abnormal liver function, renal calculi, blood disorders (including agranulocytosis and thrombocytopenia), and rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis)
- Transient myopia reported

- **Pilocarpine**

Pilocarpine is a representative miotic. Various medicines can serve as alternatives.

- **Dosage form**

- Ophthalmic drops: 2% and 4% in 15 ml bottle (hydrochloride or nitrate)

- **Uses**
 - 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
- **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)
- **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's disease
 - Withdraw treatment if symptoms of systemic toxicity develop.
 - **Skilled tasks:** Causes difficulty with dark adaptation; may cause accommodation spasm. Advise patients not to carry out skilled tasks (for example, operating machinery or driving) until vision is clear.
- **Administration**

Chronic open-angle glaucoma, by ocular instillation

- **ADULT:** 1 drop (2% or 4% solution) up to 4 times daily

Acute angle-closure glaucoma (before surgery), by ocular instillation

- **ADULT:** 1 drop (2% solution) every 10 minutes for 30– 60 minutes, then 1 drop every 1– 3 hours until intraocular pressure subsides

- **Adverse effects**

- Eye pain, blurred vision, ciliary spasm, lacrimation, myopia, brow ache
- Conjunctival vascular congestion, superficial keratitis, vitreous hemorrhage, and increased pupillary block reported; lens opacities (following prolonged use)
- Rarely systemic effects including hypertension, tachycardia, bronchial spasm, pulmonary edema, salivation, sweating, nausea, vomiting, and diarrhea

- **Timolol**

Timolol is a representative ophthalmic beta-blocker. Various medicines can serve as alternatives.

- **Dosage forms**

- Ophthalmic drops: 0.25% and 0.5% in 5 ml bottle (as maleate)

- **Uses**

- Ocular hypertension
- Chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas

- **Contraindications**

- Uncontrolled heart failure, bradycardia, heart block
- Asthma or history of obstructive pulmonary disease

- **Precautions**

- Elderly (risk of keratitis)
- In angle-closure glaucoma, use with a miotic, and not alone.
- **Interactions:** Appendix A

- **Administration**

Ocular hypertension, chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas, by ocular instillation

- **ADULT:** 1 drop (0.25% or 0.5%) twice daily

- **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 central nervous systems, may follow absorption.

21.5 MYDRIATICS

Antimuscarinics, by blocking the cholinergic effects of acetylcholine, paralyze the pupillary constrictor muscles, causing dilation of the pupil (mydriasis); and paralyze the ciliary muscles, resulting in paralysis of accommodation (cycloplegia). Mydriasis may precipitate acute angle-closure glaucoma, particularly in the elderly or far-sighted patients. In patients with dark iridic pigmentation, higher concentrations of mydriatic drugs are usually required and care should be taken to avoid overdosing.

Atropine is a long-acting antimuscarinic that is used for cycloplegic refraction procedures, particularly in children. It is also used to immobilize the ciliary muscle and iris, and to prevent formation of posterior synechiae in the treatment of inflammatory eye disorders such as iritis and uveitis.

The sympathomimetic drug **epinephrine** (adrenaline) probably acts by reducing the rate of production of aqueous humor and increasing its outflow through the trabecular network. Epinephrine is usually used with a miotic, a beta-blocker, or a systemic carbonic anhydrase inhibitor in the treatment of chronic open-angle glaucoma; however, because epinephrine is also a mydriatic, it is contraindicated for angle-closure glaucoma unless an iridectomy has been carried out.

- **Atropine**

- **Dosage forms**

- Ophthalmic drops: 0.1%, 0.5% and 1% (sulfate)
 - Ophthalmic ointment: 1%.

- **Uses**

- Iritis, uveitis
 - Cycloplegic refraction procedures

- **Contraindication**

- Angle-closure glaucoma

- **Precautions**

- Use may precipitate acute attack of angle-closure glaucoma, particularly in the elderly or far-sighted
 - Infants under 3 months (risk of systemic effects with eyedrops; eye ointment preferred)
 - **Skilled tasks:** May cause sensitivity to light and blurred vision. Advise patients not to carry out skilled tasks (for example, operating machinery or driving) until vision is clear.

- **Administration**

Cycloplegic refraction, by ocular instillation,

- **ADULT:** 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
- **CHILD** under 3 months: See Precautions.
- **CHILD** 3 months–1 year: 1 drop (0.1% solution) (1–5 years, 0.1–0.5% solution; over 5 years, 0.5–1% solution) twice daily for 1–3 days before procedure, with a further dose given 1 hour before procedure

Iritis, uveitis, by ocular instillation

- **ADULT:** 1 drop (0.5% or 1% solution) up to 4 times daily
- **CHILD:** 1 drop (0.5% or 1%) up to 3 times daily

○ **Adverse effects**

- Transient stinging and raised intraocular pressure
- Local irritation, hyperemia, edema, and conjunctivitis (on prolonged administration)
- Contact dermatitis
- Systemic toxicity (in the very young and the elderly)

SECTION 22: Oxytocics and anti-oxytocics

Several medicines may be used to modify uterine contractions. These include the oxytocic drugs, which are used to stimulate uterine contractions both in induction of labor and in the control of postpartum hemorrhage, and the beta2-adrenoceptor agonists, which are used to relax the uterus and prevent premature labor.

LML strengths and dosage forms are marked in *italic* with an asterisk.

22.1 OXYTOCICS

Termination of pregnancy

Termination of pregnancy must only be carried out where facilities for the management of complications are readily available and where the procedure is permitted under national law. In Afghanistan, medicines listed in the National Postpartum Hemorrhage Program List (like misoprostol) can be imported and used only with explicit written approval and under supervision of the MoPH National Postpartum Hemorrhage Program, under the Reproductive Health Directorate. These medicines are not for general or commercial use in the private sector. Medical abortion may be induced by the sequential use of a single oral dose of **mifepristone** (not in LML Afghanistan), followed by vaginal administration of the prostaglandin **misoprostol**. Misoprostol on its own is only a weak abortifacient and is often ineffective when used alone for the termination of pregnancy.

Mifepristone, an antiprogestogenic steroid, facilitates medical termination of pregnancy by sensitizing the myometrium to prostaglandin-induced contractions; therefore, when it is used together with misoprostol, abortion occurs in a shorter time and with a lower dose of the prostaglandin.

Induction and augmentation of labor

Prostaglandins, including misoprostol, are effective for the induction of labor. Misoprostol is usually administered in a low dose as a vaginal tablet; alternatively, it can be given by mouth but this route is less effective and requires a larger dose. Misoprostol is associated with uterine hyperstimulation; it can increase the risk of rupture and associated complications in women who have undergone multiple pregnancies or who have uterine scarring from surgery or cesarean section.

Postpartum hemorrhage

Ergometrine and **oxytocin** differ in their actions on the uterus. In moderate doses, oxytocin produces slow, generalized contractions with full relaxation in between; ergometrine produces faster contractions superimposed on a tonic contraction. High doses of both substances produce sustained tonic contractions. Oxytocin is now recommended for routine use in the control of postpartum and post-abortion hemorrhage since it is more stable than ergometrine. However, ergometrine may be used if oxytocin is not available or in emergency situations.

- **Ergometrine**

Ergometrine is subject to international control under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988). Ergometrine is a representative oxytocic drug. Various drugs can serve as alternatives.

Note: Injection requires transport by “cold chain” and refrigerated storage.

- **Dosage form**
 - Tablet: 0.2 mg (maleate)
 - Injection: 0.2 mg/ml (hydrogen maleate)/ml in 1 ml ampoule
- **Use**
 - Prevention and treatment of postpartum and post-abortion hemorrhage in emergency situations and where oxytocin not available
- **Contraindications**
 - Induction of labor
 - First and second stages of labor
 - Vascular disease; severe cardiac disease, especially angina pectoris
 - Severe hypertension; severe renal and hepatic impairment; sepsis; eclampsia
- **Precautions**
 - Cardiac disease, hypertension, hepatic impairment: Appendix E
 - Renal impairment: Appendix D
 - Multiple pregnancy, porphyria
 - **Interactions:** Appendix A
- **Dose**

Prevention and treatment of postpartum hemorrhage, by intramuscular injection

- **ADULT** and **ADOLESCENT:** 200 micrograms when the anterior shoulder is delivered or immediately after birth

Excessive uterine bleeding, by slow intravenous injection

- **ADULT and ADOLESCENT:** 250– 500 micrograms when the anterior shoulder is delivered or immediately after birth

In secondary hemorrhage after delivery, orally

- **ADULT and ADOLESCENT:** 200– 400 micrograms, 3 times a day for 3 days

- **Adverse effects**

- Nausea, vomiting, headache, dizziness, tinnitus, abdominal pain, chest pain, palpitations, dyspnea, bradycardia, transient hypertension, vasoconstriction
- Stroke, myocardial infarction, and pulmonary edema also reported

- **Methylergometrine maleate**

Methylergometrine maleate is a metabolite of methysergide maleate.

- **Dosage form**

- Tablets: 0.125 mg and 0.2 mg
- Injection: 0.2 mg/ml in 1 ml ampoule

- **Uses**

- Methylergometrine maleate has a much more powerful action on the uterus than most other ergot alkaloids, similar to that of ergometrine maleate, and is used similarly in the active management of the third stage of labor, as well as in the prevention and treatment of postpartum or postabortal hemorrhage.

- **Dose**

- In the management of the third stage of labor, it may be given in a dose of 200 micrograms intramuscularly after delivery of

the anterior shoulder or, at the latest, immediately after delivery of the infant.

- The same dose may be used for the prevention or treatment of postpartum or postabortal hemorrhage, and may be repeated every 2–4 hours as necessary up to a maximum of 5 doses.
- In emergencies, it may be given in similar doses by slow intravenous injection over at least 1 minute to reduce the risk of adverse effects, particularly hypertension.
- During the puerperium, methylergometrine maleate has been given in oral doses of 200 micrograms 3 or 4 times daily for up to a week or 125–250 micrograms up to 3 times daily.

○ **Contraindications**

- Methylergometrine maleate is contraindicated for the induction of labor or for use during the first stage of labor.
- If used at the end of the second stage of labor, before delivery of the placenta, there must be expert obstetric supervision.
- Its use should be avoided in patients with pre-eclampsia, eclampsia, or threatened spontaneous abortion.
- Porphyria: methylergometrine maleate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

○ **Precautions**

- Veno-atrial shunts or mitral valve stenosis
- **Interactions:** Appendix A

○ **Interaction**

- Halothane has been considered to diminish the effects of methylergometrine maleate on the uterus.

- **Adverse effects**

- Nausea and vomiting, abdominal pain, diarrhea, headache, dizziness, tinnitus, chest pain, palpitations, bradycardia and other cardiac arrhythmias, coronary and pulmonary edema
- Hypertension may occur, particularly after rapid intravenous dosage
- Hypotension
- Hypersensitivity reactions, including shock
- Methylergometrine maleate shows less tendency to produce gangrene than ergotamine, but ergotism has been reported and symptoms of acute poisoning are similar.

- **Misoprostol**

Misoprostol is a complementary list medicine for medical termination of pregnancy of up to 63 days' gestation where this is permitted under national law and is acceptable in Islamic culture, and for induction of labor.

- **Dosage form**

- Vaginal tablet: 25 micrograms
- Oral tablet: 200 micrograms

- **Uses**

- Induction of labor
- Medical termination of intrauterine pregnancy of up to 63 days' gestation with mifepristone

- **Contraindications**

- Induction of labor in case of: placenta previa or unexplained vaginal bleeding during pregnancy, ruptured membranes,

major cephalopelvic disproportion or fetal malpresentation, history of cesarean section or major uterine surgery, untreated pelvic infection, fetal distress, grand multiparas and multiple pregnancy, history of difficult or traumatic delivery

- **Precautions**

- Induction of labor conditions where hypotension might precipitate severe complications (for example, cerebrovascular disease or cardiovascular disease)
- **Medical termination of pregnancy:** History of cesarean section or major uterine surgery, grand multiparas (risk of rupture).
- **Important:** For warnings related to the use of mifepristone in a patient undergoing induction of abortion with a combination of misoprostol and mifepristone.

- **Dose**

Induction of labor, by vagina

- **ADULT and ADOLESCENT:** 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

Note: Should it be necessary to continue induction of labor with oxytocin, administration of oxytocin should be avoided within 8 hours of using misoprostol.

Medical termination of intrauterine pregnancy of up to 63 days' gestation, by vagina

- **ADULT and ADOLESCENT:** Misoprostol, 800 micrograms 36–48 hours after mifepristone, 200 mg as a single dose by mouth (unless abortion already complete) and individual observed 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)

- **Administration**

- For medical termination of pregnancy, oral tablets may be administered vaginally if a suitable vaginal preparation is not available.
- For induction of labor, 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.

- **Adverse effects**

- Uterine hyperstimulation, uterine rupture, fetal distress
- Less commonly in obstetric setting diarrhea, abdominal pain, dyspepsia, flatulence, nausea and vomiting, rash, dizziness

- **Oxytocin**

- **Dosage form**

- Injection: 10 IU/ml in 1 ml ampoule

- **Uses**

- Routine prevention and treatment of postpartum and post-abortion hemorrhage
- Induction of labor

- **Contraindications**

- Hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress
- Any condition where spontaneous labor or vaginal delivery inadvisable
- Avoid prolonged administration in oxytocin-resistant uterine inertia, in severe pre-eclamptic toxemia, or in severe cardiovascular disease.
- Major cephalopelvic disproportion

- **Precautions**

- Induction or enhancement of labor 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 cesarean section
- Avoid tumultuous labor if fetal death or meconium-stained amniotic fluid (risk of amniotic fluid embolism) occurs.
- Water intoxication and hyponatremia (avoid large-volume infusions and restrict fluid intake)
- Caudal block anesthesia (risk of severe hypertension due to enhanced vasopressor effect of sympathomimetics)
- **Interactions:** Appendix A

- **Dose**

Induction of labor, by intravenous infusion

- **ADULT and ADOLESCENT:** 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

Note: The dose shown above is suitable for use in the hospital, where equipment to control the infusion rate is available; alternative recommendations may be suitable for other settings; consult *Managing Complications in Pregnancy and Childbirth: A Guide for Midwives and Doctors* (Geneva: WHO, 2000).

Important: Careful monitoring of fetal heart rate and uterine motility is essential for dose titration (avoid bolus intravenous injection during labor); discontinue immediately in uterine hyperactivity or fetal distress.

Prevention of postpartum hemorrhage, by intramuscular injection

- **ADULT and ADOLESCENT:** 10 IU when the anterior shoulder is delivered or immediately after birth

Prevention of postpartum hemorrhage, by slow intravenous injection

- **ADULT and ADOLESCENT:** 5 IU when the anterior shoulder is delivered or immediately after birth

Treatment of postpartum hemorrhage, by slow intravenous injection

- **ADULT and ADOLESCENT:** 5–10 IU

Treatment of postpartum hemorrhage, by intramuscular injection

- **ADULT and ADOLESCENT:** 10 IU, followed in severe cases by a total of 40 IU, by intravenous infusion, at a rate of 0.02–0.04 IU/min; should be started after the placenta is delivered

Note: For further details on management of postpartum hemorrhage, consult *Managing Complications in Pregnancy and Childbirth: A Guide for Midwives and Doctors* (Geneva: WHO, 2000).

- **Dilution and administration**

- According to manufacturer's directions
- Prolonged intravenous administration at high doses with large volume of fluid (for example, in inevitable or missed abortion, or in postpartum hemorrhage) may cause water intoxication with hyponatremia.
- To avoid this, use electrolyte-containing diluent (not glucose), increase oxytocin concentration to reduce fluid, and restrict fluid intake by mouth; monitor fluid and electrolytes.

- **Adverse effects**

- Uterine spasm, and uterine hyperstimulation (usually with excessive doses; may cause fetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions, soft-tissue damage, or uterine rupture)
- Water intoxication and hyponatremia (with high doses and large-volume infusions)
- Nausea, vomiting, arrhythmias, rash, and anaphylactoid reactions also reported

22.2 ANTI-OXYTOCICS (TOCOLYTICS)

Premature labor

Nifedipine, a dihydropyridine calcium-channel blocker that relaxes the uterus, can be used to postpone labor in uncomplicated cases of premature labor. It can permit a delay in delivery of at least 48 hours. The greatest benefit is obtained by

using this delay to administer corticosteroid therapy or to implement other measures known to improve perinatal health.

- **Nifedipine**

- **Dosage form**

- Tablets and capsules: 10 mg and 20 mg (immediate and sustained release)

- **Uses**

- Uncomplicated premature labor between 24– 33 weeks' gestation
 - Hypertension and Raynaud's phenomenon (Section 12.3)

- **Contraindications**

- Cardiogenic shock
 - Advanced aortic stenosis
 - Within 1 month of myocardial infarction
 - Unstable or acute attacks of angina
 - Porphyria

- **Precautions**

- Stop if ischemic pain occurs shortly after starting treatment.
 - Poor cardiac reserve
 - Heart failure or significantly impaired left ventricular function
 - Severe hypotension
 - Hepatic impairment (reduce dose): Appendix E
 - Diabetes mellitus
 - Breast-feeding: Appendix C
 - Avoid grapefruit juice (may affect nifedipine metabolism).
 - **Interactions:** Appendix A

- **Dose**

Premature labor, sublingually (immediate-release capsules)

- **ADULT:** Initially 10 mg every 15 minutes if necessary, up to a maximum of 40 mg in the first hour, then 60–160 mg daily in 3–4 divided doses by mouth (sustained-release tablets), adjusted to uterine activity

Note: Different formulations of nifedipine do not have the same clinical effects, so prescribers should specify the exact formulation for the dispenser (pharmacist).

- **Adverse effects**

- Headache, flushing, dizziness, lethargy
- Tachycardia, palpitations
- Exaggerated fall in blood pressure and reflex tachycardia (may lead to myocardial or cerebrovascular ischemia)
- Gravitational edema
- Rash erythema multiforme, pruritus, urticarial
- Nausea, constipation or diarrhea
- Increased frequency of micturition
- Eye pain, visual disturbances
- Gum hyperplasia
- Asthenia, paresthesia, myalgia, tremor, gynecomastia
- Depression, telangiectasis, cholestasis, and jaundice

SECTION 23: Peritoneal dialysis solution

Solutions for peritoneal dialysis are preparations for intraperitoneal use that contain electrolytes in a concentration similar to that found in plasma, and also glucose or another suitable osmotic agent. Peritoneal dialysis solutions always contain sodium, chloride, and hydrogen carbonate (or a precursor); they may also contain calcium, magnesium, and rarely potassium.

In renal failure, hemodialysis is the preferred method to correct the accumulation of toxins, electrolytes, and fluid. Peritoneal dialysis is less efficient than hemodialysis, but it is preferred in children, diabetic patients, and patients with unstable cardiovascular disease; it is also used in patients who can manage their condition, or those who live far from a dialysis center. It is unsuitable for patients who have had significant abdominal surgery.

In peritoneal dialysis, the solution is infused into the peritoneal cavity, where exchange of electrolytes takes place by diffusion and convection, and excess fluid is removed by osmosis, using the peritoneal membrane as an osmotic membrane. There are 2 forms of peritoneal dialysis:

- *Continuous ambulatory peritoneal dialysis (CAPD)*, in which dialysis is performed manually by the patient several times each day
- *Automated peritoneal dialysis (APD)*, in which dialysis is performed by machine overnight

The main complication of peritoneal dialysis is peritonitis, which often results from poor exchange technique; infections of the catheter exit site may also occur, again because of poor technique. With long-term dialysis progressive structural changes to the peritoneal membrane occur, ultimately resulting in dialysis failure.

- **Intraperitoneal dialysis solution**

- **Dosage form**

- Isotonic and hypertonic infusion solutions in 1,000 ml bags

- **Uses**

- Correction of electrolyte imbalance, increasing blood volume, and removal of metabolites in acute renal failure

- **Contraindications**

- Abdominal sepsis, previous abdominal surgery, severe inflammatory bowel disease

- **Precautions**

- To reduce the risk of infection, caution is needed in its implementation technique.

- The dialysis solution should be warmed equivalent to body temperature level before use.
- Certain medicines may be removed with dialysis.

- **Dose**

- Varies according to clinical condition of each person and his/her blood results.

- **Adverse effects**

- Infection, including peritonitis, hernia, blood spread in the peritoneal cavity, increased blood sugar, protein malnutrition, obstruction of catheter

SECTION 24: Psychotherapeutic medicines

LML strengths and dosage forms are marked in *italic* with an asterisk.

24.1 MEDICINES USED IN PSYCHOTIC DISORDERS

Treatment of psychotic disorders such as schizophrenia is both pharmacological and psychosocial. Individual and community programs for relearning old skills and developing new ones, and for learning to cope with psychotic illness should be initiated. Classes of antipsychotic drugs include the phenothiazines (for example, chlorpromazine and fluphenazine), the butyrophenones (for example, haloperidol), the thioxanthenes (for example, flupentixol) and the newer “atypical” neuroleptics such as clozapine and risperidone. The various antipsychotic drugs do not, in general, differ in their antipsychotic activity, but rather in the range and quality of their adverse effects (see below).

Acute phase treatment

The administration of **chlorpromazine** or **haloperidol** will relieve symptoms such as thought disorders, hallucinations, and delusions, and prevent relapse. They are usually less effective in apathetic, withdrawn patients, but they can sometimes have an activating influence in such individuals. Patients with acute schizophrenia generally respond better to antipsychotic drugs than those with chronic symptoms. In the acute phase, chlorpromazine may be administered by intramuscular injection. In most cases, however, the intramuscular injection is not needed and patients can be treated with an oral dose. Haloperidol may be administered in the acute phase.

Maintenance therapy

Long-term treatment for schizophrenia may be necessary after the first episode to prevent the illness from becoming chronic. The lowest-possible dose of an antipsychotic drug that will prevent major exacerbations of florid symptoms is used for long-term management. Too rapid a dose reduction should be avoided. Intramuscular depot preparations of, for example, fluphenazine, may be used as an alternative to oral maintenance therapy, especially when compliance with oral treatment is unreliable. Exacerbations of illness in patients on maintenance drug therapy can be precipitated by stress.

Withdrawal of maintenance drug treatment requires careful surveillance since it is not possible to predict the course of the disease and the patient may suffer a relapse if treatment is withdrawn inappropriately. Furthermore, the need for continuation of treatment may not be evident on withdrawal of treatment because relapse may be delayed for several weeks.

Adverse effects

Adverse effects are very common with long-term administration of antipsychotic medicines (for specific details, *see under* each individual drug). Treatment of all patients on antipsychotics must be carefully and regularly reviewed. Hypotension and interference with temperature regulation, neuroleptic malignant syndrome, and bone marrow depression are the most life-threatening adverse effects of

antipsychotics. Both hypotension and interference with temperature regulation are dose-related, and can result in dangerous falls and hypothermia in the elderly. This aspect must be considered before prescribing these drugs for patients over 70 years of age.

Extrapyramidal symptoms are the most troublesome adverse effects of antipsychotics and are caused most frequently by the piperazine phenothiazines such as fluphenazine, the butyrophenones such as haloperidol, and the depot preparations; the newer “atypical” antipsychotics cause fewer extrapyramidal symptoms than other antipsychotics. Although easily recognized, extrapyramidal symptoms are not so easy to predict because they depend on the dose and patient susceptibility as well as the drug.

Extrapyramidal symptoms consist of

- *Parkinsonian* symptoms (including tremor), which may occur more commonly in adults or the elderly and may appear gradually
- *Dystonia* (abnormal face and body movements) and dyskinesia, which occur more commonly in children or young adults and appear after only a few doses
- *Akathisia* (restlessness), which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated

- *Tardive dyskinesia* (rhythmic, involuntary movements of tongue, face, and jaw), which usually develops on long-term therapy or with high dosage, but it may develop on short-term treatment with low doses—short-lived tardive dyskinesia may occur after withdrawal of the drug

In addition, *neuroleptic malignant syndrome*, which is characterized by hypothermia, fluctuating levels of consciousness, muscular rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating, and urinary incontinence, is a rare adverse effect of haloperidol and chlorpromazine. It is managed by discontinuing the antipsychotic, correcting fluid and electrolyte defects, and by giving bromocriptine and sometimes dantrolene.

- **Chlorpromazine**

Chlorpromazine is a representative antipsychotic. Various medicines can serve as alternatives.

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.

- **Dosage form**

- Tablets: 25 mg, 50 mg, and 100 mg (hydrochloride)
- Injection: 25 mg/ml (hydrochloride in 2 ml ampoule)

- **Uses**

- Schizophrenia and other psychotic disorders, mania, psychomotor agitation, and violent behavior
- Adjunct in severe anxiety, in severe vomiting (Section 17.2)

- **Contraindications**

- Impaired consciousness due to central nervous system depression
- Bone marrow depression
- Pheochromocytoma

- **Precautions**

- Cardiovascular and cerebrovascular disorders
- Respiratory disease
- Parkinsonism
- Epilepsy
- Acute infections
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Renal impairment (avoid if severe): Appendix D

- Hepatic impairment (avoid if severe): Appendix E
- History of jaundice
- Leukopenia (monitor blood counts if unexplained fever or infection occur)
- Hypothyroidism, myasthenia gravis
- Prostatic hypertrophy
- Angle-closure glaucoma
- The elderly (particularly in very hot or very cold weather; reduce dose)
- Avoid abrupt withdrawal
- Patients should remain supine and blood pressure monitored for 30 minutes after intramuscular injection (risk of hypotension)
- **Interactions:** Appendix A
- **Skilled tasks:** May impair ability to perform skilled tasks (for example operating machinery or driving)

○ **Dose**

Schizophrenia and other psychoses, mania, psychomotor agitation, violent behavior, severe anxiety (adjunct), by mouth

- **ADULT:** 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): One-third to one-half of adult dose
- **CHILD** (childhood schizophrenia and autism) 1–5 years: 500 micrograms/kg every 4–6 hours (max. 40 mg daily)
- **CHILD** 6–12 years: One-third to one-half of adult dose (max. 75 mg daily)

For relief of acute symptoms, by deep intramuscular injection

- **ADULT:** 25–50 mg every 6–8 hours
- **CHILD:** 1–12 years, 500 micrograms/kg every 6–8 hours (1–5 years, max. 40 mg daily; 6–12 years, max. 75 mg daily) (see also Precautions; Adverse effects)

○ **Adverse effects**

- Extrapyramidal symptoms and on prolonged administration, occasionally potentially irreversible tardive dyskinesias (see introductory note above)
- Hypothermia (occasionally pyrexia), drowsiness, apathy, pallor, nightmares, dizziness, excitement, insomnia, headache, confusion, depression
- More rarely, agitation, EEG changes, convulsions, and nasal congestion
- Anticholinergic symptoms including dry mouth, constipation, blurred vision, and difficulty in micturition
- Hypotension, tachycardia, and arrhythmias

- ECG changes
- Respiratory depression
- Menstrual disturbances, galactorrhea, gynecomastia, impotence, weight gain
- Sensitivity reactions such as agranulocytosis, leukopenia, leukocytosis, hemolytic anemia, photosensitization, contact sensitization and rash, jaundice, and alterations in liver function
- Neuroleptic malignant syndrome
- Lupus erythematosus–like syndrome
- Corneal and lens opacities, and purplish pigmentation of the skin, cornea, and retina (with prolonged high dosage)
- Intramuscular injection may be painful and cause hypotension and tachycardia (see Precautions) and nodule formation.

- **Fluphenazine**

Fluphenazine is a representative depot antipsychotic for use when compliance is unlikely to be reliable. Various medicines can serve as alternatives.

- **Dosage form**

- Injection solution (oily): 1 mg/ml in 1 ml ampoule

- **Uses**

- Maintenance treatment of schizophrenia and other psychoses

- **Contraindications**

- Children
- Confusional states
- Impaired consciousness due to central nervous system depression
- Parkinsonism
- Intolerance to antipsychotics
- Depression
- Bone marrow depression
- Pheochromocytoma
- Marked cerebral arteriosclerosis

- **Precautions**

- Treatment requires careful monitoring for optimum effect
- Administer an initial small test dose as adverse effects are prolonged
- Extrapyramidal symptoms occur frequently
- When transferring from oral to depot therapy, dosage by mouth should be reduced gradually
- Cardiovascular and cerebrovascular disorders, respiratory disease
- Epilepsy
- Acute infections

- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Renal impairment (avoid if severe): Appendix D
- Hepatic impairment (avoid if severe): Appendix E
- History of jaundice
- Leukopenia (monitor blood counts if unexplained fever or infection occur)
- Hypothyroidism
- Myasthenia gravis
- Prostatic hypertrophy
- Angle-closure glaucoma
- Elderly (reduce dose in very hot or very cold weather)
- **Interactions:** Appendix A
- **Skilled tasks:** May impair ability to perform skilled tasks (for example, operating machinery or driving)

○ **Dose**

Maintenance in schizophrenia and other psychoses, by deep intramuscular injection into gluteal muscle

- **ADULT:** Test dose of 12.5 mg (6.25 mg in the **ELDERLY**), then after 4–7 days, 12.5–100 mg repeated at intervals of 2–5 weeks, adjusted according to response

- **CHILD:** Not recommended

- **Administration**

- According to manufacturer's directions

- **Adverse effects**

- As for chlorpromazine (see above), but less sedative effects, fewer hypotensive and anticholinergic symptoms and a higher incidence of extrapyramidal symptoms (most likely to occur a few hours after injection and continue for about 2 days but may be delayed)
- Systemic lupus erythematosus
- Pain at injection site, and occasionally erythema, swelling, nodules
- Inappropriate antidiuretic hormone secretion, edema

- **Haloperidol**

Haloperidol is a representative antipsychotic. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 0.5 mg, 2 mg, and 5 mg
- Injection: 5 mg in 1 ml ampoule
- Oral drops: 2 mg/ml

- **Uses**

- Schizophrenia and other psychotic disorders, mania, short-term adjunctive management of psychomotor agitation, violent behavior, and severe anxiety

- **Contraindications**

- Impaired consciousness due to central nervous system depression
- Bone marrow depression
- Pheochromocytoma
- Porphyria
- Basal ganglia disease

- **Precautions**

- Cardiovascular and cerebrovascular disorders, respiratory disease, Parkinsonism, epilepsy, acute infections
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Renal and hepatic impairment (avoid if severe): Appendices D and E
- History of jaundice, leukopenia (blood count required if unexplained fever or infection)
- Hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma

- Also sub-arachnoid hemorrhage and metabolic disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia
 - Elderly (particularly in very hot or very cold weather)
 - Children and adolescents
 - Avoid abrupt withdrawal.
 - Patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection
 - **Interactions:** Appendix A
 - **Skilled tasks:** May impair ability to perform skilled tasks (for example, operating machinery or driving)
- **Dose**

Schizophrenia and other psychoses, mania, short-term adjunctive management of psychomotor agitation, violent behavior, and severe anxiety, by mouth

- **ADULT:** 1.5–3 mg 2–3 times daily (one-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)
- **CHILD:** 25–50 micrograms/kg daily in 2 divided doses (max. 10 mg daily)

Acute psychotic conditions, by intramuscular injection

- **ADULT:** Initially 2–10 mg (one-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
- **CHILD:** Not recommended
- **Adverse effects**
 - As for chlorpromazine (see above), but fewer sedative effects and fewer hypotensive and anticholinergic symptoms
 - Rarely pigmentation and photosensitivity reactions
 - Extrapyrarnidal symptoms are common, particularly acute dystonia and akathisia (especially in thyrotoxic patients)
 - Rarely weight loss, and hypoglycemia, inappropriate antidiuretic hormone secretion

24.2 MEDICINES USED IN MOOD DISORDERS

Mood disorders can be classified as depression (unipolar disorder) or mania; alternating episodes of mania and depression (manic depression) are termed bipolar disorder.

Electroconvulsive therapy (ECT) has been shown to be rapidly effective in the urgent treatment of severe depression. Counseling and psychotherapy have an important role in treating some forms of depression.

24.2.1 Medicines used in depressive disorders

Tricyclic and related antidepressants and selective serotonin reuptake inhibitors (SSRIs) are the most widely used drugs in the treatment of depressive disorders. The response to antidepressant therapy is usually delayed, with a lag period of up to 2 weeks and at least 6 weeks before maximum improvement occurs. It is important to use doses that are sufficiently high for effective treatment, but not so high as to cause toxic effects. Low doses should be used for initial treatment in the elderly. The use of more than one antidepressant at a time is not recommended since this does not enhance effectiveness and it may result in enhanced adverse effects or interactions.

Patients should be reviewed every 1–2 weeks at the start of treatment.

Treatment should be continued for at least 4 weeks (6 weeks in the elderly) before considering a change to another antidepressant because of problems with suitability or efficacy. In the case of a partial response, treatment may be continued for a further 2 weeks (or possibly longer in elderly patients as they may take longer to respond). Remission usually occurs after 3–12 months.

Treatment at full therapeutic dose should be continued for at least 6 months, but preferably up to 12 months after resolution of symptoms (about 12 months in the elderly). Treatment should not be withdrawn prematurely, otherwise symptoms are likely to recur. Patients with a history of recurrent depression should continue to receive maintenance treatment (for at least 5 years and possibly indefinitely).

Lithium may be used as an alternative to antidepressants for maintenance

treatment. The lithium dose should be reduced gradually over about 4 weeks, or even longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

Tricyclic and related antidepressants can be divided into those with lesser sedative effect. Those with sedative properties include amitriptyline and those with a less sedative effect include imipramine. These drugs are most effective in the treatment of depression associated with psychomotor and physiological disturbances. Adverse effects include anticholinergic (more correctly, antimuscarinic) symptoms of dry mouth, blurred vision, constipation, and urinary retention. Arrhythmias and heart block can also occur. Minimal quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular effects are dangerous in overdose. **Amitriptyline** in overdose is associated with a high rate of fatality.

Fluoxetine is a SSRI that characteristically causes gastrointestinal disturbances, sleep disturbances, and hypersensitivity reactions including rash (may be a sign of an impending serious systemic reaction and discontinuation should be considered) but they are less sedating and have fewer anticholinergic (antimuscarinic) and cardiotoxic effects than tricyclic antidepressants. The SSRIs are less toxic in overdose than the older tricyclic compounds, but there is some concern that SSRIs may increase suicidal ideation, especially in children and adolescents.

- **Amitriptyline**

Amitriptyline is a representative tricyclic antidepressant. Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 10 mg, 25 mg, and 100 mg (hydrochloride)

- **Use**

- Moderate-to-severe depression

- **Contraindications**

- Recent myocardial infarction, arrhythmias (especially heart block)
- Manic phase in bipolar disorders
- Severe liver disease
- Children
- Porphyria

- **Precautions**

- Cardiac disease (see *also* Contraindications above)
- History of epilepsy
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- Elderly (reduce dose)

- Hepatic impairment: Appendix E
- Thyroid disease
- Pheochromocytoma
- History of mania or psychoses (may aggravate psychotic symptoms)
- Angle-closure glaucoma, history of urinary retention; concurrent electroconvulsive therapy
- Avoid abrupt withdrawal.
- Anesthesia (increased risk of arrhythmias and hypotension)
- **Interactions:** Appendix A
- **Skilled tasks:** May impair ability to perform skilled tasks (for example operating machinery or driving)

- **Dose**

Depression, by mouth

- **ADULT:** Initially 75 mg daily (30–75 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
- **CHILD** under 16 years: Not recommended

- **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, syncope; sweating, tremor, rash, and hypersensitivity reactions (urticaria, photosensitivity)
- Behavioral 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, gynecomastia and galactorrhea
- Convulsions, movement disorders and dyskinesias, dysarthria, paresthesia, taste disturbances, tinnitus, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatremia (may be due to inappropriate antidiuretic hormone secretion)
- Abnormal liver function test
- In overdose excitement, restlessness, and marked anticholinergic effects (severe symptoms include unconsciousness, convulsions, myoclonus, hyperreflexia, hypotension, acidosis, and respiratory

and cardiac depression with arrhythmias; high rate of fatality; see
also introductory note above)

- **Fluoxetine**

- **Dosage form**

- Tablet: 20 mg (hydrochloride)

- **Uses**

- Moderate-to-severe major depression
 - Bulimia nervosa

- **Contraindication**

- Manic phase

- **Precautions**

- Epilepsy
 - Cardiac disease, bleeding disorders, diabetes mellitus
 - Susceptibility to angle-closure glaucoma
 - History of mania (discontinue if patient entering manic phase)
 - Concurrent electroconvulsive therapy (prolonged seizures reported)
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Hepatic impairment: Appendix E

- Avoid abrupt withdrawal.
- Children and adolescents (increased risk of suicide)
- **Interactions:** Appendix A
- **Skilled tasks:** May impair ability to perform skilled tasks (for example operating machinery or driving)

- **Dose**

Depression, by mouth

- **ADULT:** Initially 20 mg once daily, increased as necessary after 3 weeks to a maximum of 80 mg daily (60 mg daily in the elderly); usual maintenance dose in the range is 20–60 mg once daily (20–40 mg once daily in the elderly)

Bulimia nervosa, by mouth

- **ADULT** over 18 years: 60 mg once daily

Obsessive-compulsive disorder, by mouth

- **ADULT** over 18 years: 20 mg once daily; increased gradually if necessary to maximum of 60 mg once daily; **ELDERLY:** usual maximum 40 mg

Note: Consider the long duration of action of fluoxetine when adjusting dosage.

- **Adverse effects**

- Gastrointestinal disturbances, anorexia with weight loss, postural hypotension, pharyngitis, dyspnea, headache, sleep disturbances, dizziness, ataxia, tremor, convulsions (consider discontinuation)
- Altered blood glucose control in people with diabetes
- Taste disturbances, urinary retention and frequency, sexual dysfunction, galactorrhea, arthralgia, myalgia, visual disturbances, photosensitivity, chills, increased sweating, dry mouth, alopecia, rash (may be a sign of serious systemic reaction; consider discontinuation), urticaria, angioedema, vasculitis, anaphylaxis
- Yawning, idiosyncratic hepatitis, pulmonary fibrosis, restlessness, akathisia, hallucinations, manic reactions, confusion, agitation, anxiety, depersonalization, panic attacks, suicidal ideation, hyponatremia, movement disorders and dyskinesias, bleeding disorders including ecchymosis; serotonin syndrome, and erythema multiforme (leading to Stevens-Johnson syndrome or toxic epidermal necrolysis) also reported; on withdrawal dizziness, nausea, anxiety, headaches, paresthesia, sleep disturbances, fatigue, agitation, tremor, and sweating (particularly if withdrawn too abruptly)

- **Imipramine**

- **Dosage form**

- Tablets: 10 mg and 25 mg (hydrochloride)

- **Uses**

- Depressive illness
- Nocturnal enuresis in children (may be considered for children who have not responded to all other treatment and have undergone specialist assessment, but behavioral disturbances can occur and relapse is common after withdrawal; treatment should not normally exceed 3 months unless a physical examination is made and the child is fully reassessed; toxicity following overdose is a particular concern)

- **Contraindications**

- Tricyclic and related antidepressants in the immediate recovery period after myocardial infarction, in arrhythmias (particularly heart block), and in the manic phase of bipolar disorder
- Avoid in acute porphyria.

- **Precautions**

- Cardiovascular disease (see *also* Contraindications above)
- Hyperthyroidism and pheochromocytoma
- Epilepsy and diabetes

- Prostatic hypertrophy, chronic constipation, increased intraocular pressure, urinary retention, or those with a susceptibility to angle-closure glaucoma
- Significant risk of suicide, or a history of psychosis or bipolar disorder
- Manic phase
- Elderly (low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side effects)
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- ***Interactions:*** Appendix A

○ **Dose**

Depression

- **ADULT:** Initially up to 75 mg daily in divided doses increased gradually to 150–200 mg (up to 300 mg in hospital patients); up to 150 mg may be given as a single dose at bedtime
- **ELDERLY:** Initially 10 mg daily, increased gradually to 30–50 mg daily
- **CHILD:** Not recommended

Nocturnal enuresis

- **CHILD** 7–8 years: 25 mg
- **CHILD** 8–11 years: 25–50 mg
- **CHILD** over 11 years: 50–75 mg at bedtime; maximum period of treatment (including gradual withdrawal) 3 months—full physical examination before further course

- **Adverse effects**

- Palpitation, flushing, restlessness, headache, fatigue
- Very rarely abdominal pain, stomatitis, hypertension, edema, cardiac decompensation, allergic alveolitis, aggression, myoclonus, peripheral vasospasm, and mydriasis

- **Nortriptyline**

- **Dosage form**

- Tablets: 10 mg and 25 mg

- **Uses**

- Depressive illness
- Neuropathic pain [unlicensed]

- **Contraindications**

- In the immediate recovery period after myocardial infarction, in arrhythmias (particularly heart block), and in the manic phase of bipolar disorder
- Avoid treatment in acute porphyria.

- **Precautions**

- Cardiovascular disease
- Hyperthyroidism and pheochromocytoma
- Epilepsy and diabetes
- Prostatic hypertrophy, chronic constipation, increased intraocular pressure, urinary retention, or those with a susceptibility to angle-closure glaucoma
- Significant risk of suicide, or a history of psychosis or bipolar disorder
- Manic phase
- Elderly (low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side effect)
- Hepatic impairment: Appendix E
- Renal impairment: Appendix D
- Pregnancy: Appendix B
- Breast-feeding: Appendix C

- **Dose**

Depression

- **ADULT:** Low dose initially increased as necessary to 75–100 mg daily in divided doses or as a single dose (max. 150 mg daily)
- **ADOLESCENT** and **ELDERLY:** 30–50 mg daily in divided doses
- **CHILD:** Not recommended for depression

Neuropathic pain [unlicensed]

- **ADULT:** Initially 10 mg daily at night, gradually increased if necessary to 75 mg daily; higher doses under specialist supervision

- **Adverse effects**
 - Arrhythmias and heart block, postural hypotension, tachycardia, and ECG changes
 - Anxiety, dizziness, agitation, confusion, sleep disturbances, irritability, and paresthesia
 - Drowsiness
 - Convulsions, hallucinations, delusions, mania, and hypomania
 - Rarely extrapyramidal symptoms including tremor and dysarthria
 - Dry mouth, blurred vision (very rarely precipitation of angle-closure glaucoma), constipation (rarely leading to paralytic ileus, particularly in the elderly), and urinary retention
 - Breast enlargement, galactorrhea, and gynecomastia
 - Sexual dysfunction
 - Changes in blood sugar, increased appetite, and weight gain
 - Anorexia and weight loss
 - Hepatic and hematological reactions
 - Hyponatremia
 - Nausea, vomiting, taste disturbance, tinnitus, rash, urticaria, pruritus, photosensitivity, alopecia, and sweating

- The patient should be encouraged to persist with treatment, as some tolerance to these side effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible. Neuroleptic malignant syndrome may, very rarely, occur in the course of antidepressant drug treatment. Suicidal behavior has been linked with antidepressants; also abdominal pain, stomatitis, diarrhea, hypertension, edema, flushing, restlessness, fatigue, and mydriasis.

24.2.2 Medicines used in bipolar disorders

Treatment of bipolar disorders has to take account of 3 stages: treatment of the acute episode, treatment during the continuation phase, and prophylaxis to prevent further episodes. **Lithium** is effective in acute mania but symptomatic control of the florid symptoms with an antipsychotic or a benzodiazepine is often necessary while waiting for the antimania drug to exert its effect.

Benzodiazepines may be given during the initial stages until lithium becomes effective, but they should not be used for long periods because of the risk of dependence. Lithium may be given concurrently with antipsychotics, but treatment with the antipsychotic should be tailed off as lithium begins to exert its effect. However, there is a risk of neurotoxicity and increased extrapyramidal disorders when lithium and antipsychotics are used concurrently (Appendix A). Alternatively, lithium therapy may be delayed until the patient's mood is stabilized

with the antipsychotic. Lithium is the mainstay of the treatment of bipolar disorders but its narrow therapeutic range is a disadvantage. **Valproic acid** (sodium valproate) is effective and **carbamazepine** may also be used.

Treatment of depressive episodes in bipolar disorders mostly involves combination treatment, using either lithium or valproic acid together with a tricyclic antidepressant. Increased adverse effects are a problem, which may compromise treatment.

Lithium prophylaxis should usually only be undertaken with specialist advice and the likelihood of recurrence considered. Long-term lithium therapy has been associated with thyroid disorders and mild cognitive and memory impairment. Patients should continue the treatment for longer than 3-5 years only if benefit persists. Withdrawal appears to produce high levels of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a few weeks and patients warned of possible relapses if lithium is discontinued too abruptly.

Lithium salts have a narrow therapeutic: toxic ratio and should only be prescribed if there are facilities for monitoring serum lithium concentrations. Doses are adjusted to achieve serum lithium concentrations 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. The optimum range for each patient should be determined.

Overdosage, usually associated with serum lithium concentration of over 1.5 mmol/L, may be fatal; toxic effects include coarse tremor, ataxia, dysarthria, nystagmus, renal impairment, and convulsions. If any of these effects occur, treatment should be stopped and serum lithium concentration determined. In mild overdosage, large amounts of sodium salts and fluid should be given to reverse the toxicity; in severe toxicity, hemodialysis may be required.

For patients who are unresponsive to or intolerant of lithium, **carbamazepine** may be used in the prophylaxis of bipolar disorder particularly in those with rapid cycling manic-depressive illness (more than 4 affective episodes per year).

- **Carbamazepine**

- **Dosage form**

- Tablets: 100 mg and 200 mg

- **Uses**

- Prophylaxis of bipolar disorder unresponsive to or intolerant of lithium
 - Epilepsy, trigeminal neuralgia (Section 5)

- **Contraindications**

- See Section 5.

- **Precautions**

- See Section 5.

- **Dose**

Prophylaxis of bipolar disorder, by mouth

- **ADULT:** Initially 400 mg daily in divided doses increased until symptoms are controlled up to a maximum of 1.6 g daily; usual maintenance dose in range, 400–600 mg daily

- **Adverse effects**

- See Section 5.

- **Valproic acid**

- **Dosage form**

- Tablets: 200 mg, 250 mg, and 500 mg
- Syrup: 250 mg/5 ml

- **Uses**

- Acute mania
- Epilepsy (Section 5)

- **Contraindications**

- See Section 5.

- **Precautions**
 - See Section 5.
- **Dose**

Acute mania, by mouth

- **ADULT:** Initially 700 mg daily in divided doses, increased as quickly as possible to achieve the optimal response (max. 70 mg/kg daily but monitor patient closely if dose is greater than 52 mg/kg daily)

- **Adverse effects**
 - See Section 5.

24.3 MEDICINES USED IN GENERALIZED ANXIETY AND SLEEP DISORDERS

The most widely used anxiolytics and hypnotics are the benzodiazepines. Treatment of anxiety should be limited to the lowest effective dose for the shortest possible time. The cause of insomnia should be established and appropriate treatment for underlying factors instituted before hypnotics are considered. Hypnotics may be of value for a few days but rarely longer than a week.

Tolerance and dependence (both physical and psychological) and subsequent difficulty in withdrawing the drug may occur after regular use for more than a few weeks. Patients with chronic anxiety, alcohol or drug dependence, or those with personality disorders are more likely to become dependent. Anxiolytics and hypnotics such as **diazepam** should be prescribed in carefully individualized dosage regimens, and use should be limited to control of acute conditions such as panic attacks and acute anxiety and severe, incapacitating insomnia. There is usually no justification for prolonging treatment with anxiolytics and hypnotics for more than 1–2 weeks.

If used for longer periods, withdrawal should be by gradual reduction of the dose over a period of weeks or months, as abrupt discontinuation may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens. The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine and within a few hours in the case of a short-acting one. The syndrome is characterized by insomnia, anxiety, loss of appetite and body weight, tremor, perspiration, tinnitus, and perceptual disturbances. These symptoms may be similar to the original complaint and thus may encourage further prescribing. Some symptoms may continue for weeks or months after stopping benzodiazepines.

Patients should be warned that their ability to drive or operate machinery may be impaired and that the effects of alcohol may be enhanced.

- **Alprazolam**

- **Dosage form**

- Tablets: 0.25 mg, 0.5 mg, and 1 mg

- **Use**

- Short-term use in anxiety

- **Contraindications**

- *See under* Diazepam.

- **Precaution**

- *See under* Diazepam.

- **Dose**

- **ADULT:** 250–500 micrograms 3 times daily (**ELDERLY** or **DEBILITATED:** 250 micrograms 2–3 times daily), increased if necessary to a total of 3 mg daily
 - **CHILD:** Not recommended

- **Adverse effects**

- *See under* Diazepam.

- **Chlordiazepoxide**

- **Dosage form**

- Tablets and capsules: 5 mg and 10 mg (hydrochloride)

- **Uses**

- Short-term use in anxiety (2–4 weeks only)
 - Adjunct in acute alcohol withdrawal therapy to attenuate alcohol withdrawal symptoms

- **Contraindications**

- *See under* Diazepam.

- **Precaution**

- *See under* Diazepam.

- **Dose**

- Anxiety*

- **ADULT:** 10 mg 3 times daily increased if necessary to 60–100 mg daily in divided doses
 - **ELDERLY** or **DEBILITATED:** One-half of adult dose
 - **CHILD:** Not recommended

- Alcohol withdrawal in primary care*

- **ADULT:** 10– 50 mg 4 times daily, gradually reduced over 5–10 days

- **Adverse effects**

- *See under* Diazepam.

- **Diazepam**

Diazepam is a representative benzodiazepine anxiolytic and hypnotic.

Various medicines can serve as alternatives.

- **Dosage form**

- Tablets: 2 mg, 5 mg, and 10 mg
- Injection: 5 mg/ml in 2 ml

- **Uses**

- Short-term treatment of anxiety and insomnia
- Status epilepticus, recurrent seizures
- Febrile convulsions, adjunct in acute alcohol withdrawal (Section 5)
- Premedication (Section 1.3)

- **Contraindications**

- Respiratory depression
- Acute pulmonary insufficiency
- Sleep apnea

- Severe hepatic impairment
- Myasthenia gravis
- **Precautions**
 - Respiratory disease
 - Muscle weakness
 - History of alcohol or drug abuse, marked personality disorder
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - Elderly or debilitated (reduce dose)
 - Hepatic impairment (reduce dose but avoid if severe): Appendix E
 - Renal impairment: Appendix D
 - Avoid prolonged use and abrupt withdrawal.
 - Porphyria
 - **Interactions:** Appendix A
 - **Skilled tasks:** May impair ability to perform skilled tasks (for example operating machinery or driving)
- **Administration**
 - Absorption following intramuscular injection is slow and erratic.
 - This route should only be used if neither oral nor intravenous administration is possible.
 - Slow intravenous injection into large vein reduces risk of thrombophlebitis.

- Resuscitation equipment must be available.
- **Precautions for intravenous infusion**
 - Intravenous infusion of diazepam is potentially hazardous (especially if prolonged), calling for close and constant observation and is best carried out in a specialist center with intensive care facilities.
 - Prolonged intravenous infusion may lead to accumulation and delay recovery.
- **Dose**

Anxiety, by mouth

- **ADULT:** 2 mg 3 times daily, increased if necessary to 15–30 mg daily in divided doses (reduced to one-half of the adult dose in the **ELDERLY** and **DEBILITATED** patients)

Insomnia, by mouth

- **ADULT:** 5–15 mg at bedtime

Status epilepticus, febrile convulsions, and convulsions due to

poisoning, by intravenous injection

- **ADULT:** 10 mg at a rate of 1 ml (5 mg) per minute, repeated once after 10 minutes if necessary

- **CHILD** under 12 years: 300–400 micrograms/kg (max.10 mg)
[unlicensed dose], repeated once after 10 minutes if necessary
- **Adverse effects**
 - Drowsiness and light-headedness the next day
 - Confusion and ataxia (especially in the elderly)
 - Amnesia
 - Dependence
 - Paradoxical increase in aggression
 - Muscle weakness
 - Occasionally headache, vertigo, salivation changes, gastrointestinal disturbances, visual disturbances, dysarthria, tremor, changes in libido, incontinence, and urinary retention
 - Blood disorders and jaundice
 - Skin reactions
 - Raised liver enzymes

24.4 MEDICINES USED FOR OBSESSIVE-COMPULSIVE DISORDERS AND PANIC ATTACKS

Obsessive-compulsive disorders can be treated with a combination of pharmacological, behavioral, and psychological treatments. Antidepressants such as **clomipramine**, which inhibit reuptake of serotonin, have been found to be effective. Panic attacks may be treated with behavioral or cognitive therapy. If this management fails, drug therapy may be tried. Some tricyclic antidepressants, including clomipramine, or SSRIs can reduce frequency of

attacks or prevent them completely. Benzodiazepines (Section 24.3) may be used in panic attacks resistant to antidepressants.

- **Clomipramine**

- **Dosage form**

- Tablets and capsules: 25 mg and 50 mg (hydrochloride)

- **Uses**

- Panic attacks
 - Depressive illness, phobic and obsessional states
 - Adjunctive treatment of cataplexy associated with narcolepsy

- **Contraindications**

- Recent myocardial infarction, arrhythmias (especially heart block)
 - Manic phase in bipolar disorders
 - Severe liver disease
 - Children
 - Porphyria

- **Precautions**

- Cardiac disease (see *also* Contraindications above)
 - History of epilepsy
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C

- Elderly
- Hepatic impairment: Appendix E
- Thyroid disease
- Pheochromocytoma
- History of mania, and psychoses (may aggravate psychotic symptoms)
- Angle-closure glaucoma
- History of urinary retention
- Concurrent electroconvulsive therapy
- Avoid abrupt withdrawal
- Anesthesia (increased risk of arrhythmias and hypotension)
- **Interactions:** Appendix A
- **Skilled tasks:** May impair ability to perform skilled tasks (for example operating machinery or driving)

○ **Dose**

Phobic and obsessional states, by mouth

- **ADULT:** Initially 25 mg daily, usually at bedtime (10 mg daily in the elderly) increased over 2 weeks to 100–150 mg daily
- **CHILD:** Not usually recommended

Depression (but not recommended)

- **ADULT** and **CHILD** over 16 years: Initially 75 mg (elderly and adolescents 30–75 mg) daily in divided doses or as a single dose at bedtime increased gradually as necessary to 150–200 mg

Adjunctive treatment of cataplexy associated with narcolepsy

- **ADULT** over 18 years: Initially 10 mg daily, gradually increased until satisfactory response (range 10–75 mg daily)

○ **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)
- Behavioral 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, gynecomastia, and galactorrhea

- Convulsions, movement disorders and dyskinesias, dysarthria, paresthesia, taste disturbances, tinnitus, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatremia (may be due to inappropriate antidiuretic hormone secretion)
- Abnormal liver function test, diarrhea; hair loss

24.5 MEDICINES USED IN SUBSTANCE-DEPENDENCE

PROGRAMS

The management of opioid dependence requires medical, social, and psychological treatment; access to multidisciplinary care is valuable. Treatment with opioid substitutes should be initiated under the supervision of an appropriately qualified health-care worker as part of an established treatment program. **Methadone**, an opioid agonist, can be substituted for opioids such as diamorphine (heroin), to prevent the onset of withdrawal symptoms; it is itself addictive and should only be prescribed for those who are physically dependent on opioids. Methadone is administered in a single daily dose; the dose is determined by the degree of dependence.

Buprenorphine is a partial opioid agonist and may be used as an alternative to methadone; it should be prescribed only for those who are already physically dependent on opioids. It can be used as substitution therapy for patients with moderate opioid dependence; in patients dependent on high doses of opioids, buprenorphine may precipitate withdrawal due to its partial antagonist properties;

it is also addictive and in these patients the opioid dose should be reduced gradually before initiating therapy with buprenorphine.

- **Buprenorphine**

- **Dosage form**

- Tablets: 2 mg and 8 mg

- **Use**

- Treatment of drug addicts

- **Precaution**

- It is safe in majority of cases in the treatment of drug addicts.

- **Dose**

- Maximum and minimum dose is 12–34 mg and can be administered 16 mg daily.

- **Adverse effects**

- Nausea, vomiting, constipation, sleep disorders, headache, confusion

- **Methadone**

Methadone is a representative opioid agonist for use in opioid dependence. Bupremorphine can serve as an alternative.

- **Dosage form**

- Tablets: 5 mg and 10 mg
- Injection: 10 mg/ml in 1 ml ampoule
- Oral liquid: 5 mg/ml and 10 mg/ml

Note: 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.

- **Use**

- Adjunct in treatment of opioid dependence

- **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: Appendix D

- Hepatic impairment: Appendix E
- Risk of toxicity in children and non-dependent 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: Appendix B
- Breast-feeding: Appendix C
- Overdosage (Section 4.2)
- ***Interactions:*** Appendix A

Incompatibility: Syrup preserved with hydroxybenzoate (parabens) esters may be incompatible with methadone hydrochloride.

○ **Dose**

Adjunct in treatment of opioid dependence

- **ADULT:** By mouth, initially 10–40 mg daily, increased by up to 10 mg daily (max. weekly increase 30 mg) until no signs of withdrawal or intoxication; usual maintenance dose in range, 60–120 mg daily
- **CHILD:** Not recommended (*see also under* Precautions above)

○ **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)

- **Opium tincture**

- **Dosage form**

- Oral solution: 10%

- **Uses**

- Opium tincture is useful in the treatment of diarrhea.

- **Contraindications**

- **It is not prescribed to children.**
 - This drug should not be administered until gastrointestinal contents are emptied from the stomach in diarrhea caused by poisoning.

- **Precautions**

- Using this drug may cause addiction.
 - Opium should be used with minimum effective dosage and for little time so as to prevent the development of tolerance and addiction.
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interactions:** Appendix A

- **Dose**

- **ADULT:** Oral dose of 0.6 ml 4 times daily

- **Adverse effects**

- Constipation, nausea, and vomiting happen in some patients.
 - Some patients have reported itchy skin and desquamation.

SECTION 25: Medicines acting on the respiratory tract

LML strengths and dosage forms are marked in italic with an asterisk.

25.1 ANTI-ASTHMATICS AND MEDICINES FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

ASTHMA

Asthma is a chronic inflammatory disease characterized by episodes of reversible pulmonary obstruction due to bronchial hyperresponsiveness; inflammation may lead to irreversible obstruction in a few patients. A classification system for asthma, based on severity before the start of treatment and disease progression, is of importance when decisions have to be made about its management. Asthma can be divided by its severity into intermittent, mild persistent, moderate persistent, and severe persistent. These are useful in the management of the disease since therapy has a stepwise approach, which must be discussed with the patient before commencing therapy. The level of therapy is increased as the severity of the asthma increases with stepping-down if control is sustained.

Medications for asthma can be administered in several different ways, including by inhalation, orally or parenterally (by subcutaneous, intramuscular, or intravenous injection).

Inhalation

The main advantage of delivering drugs directly into the airways via inhalation is that high concentrations can be delivered more effectively and rapidly to the airways, and systemic adverse effects avoided or minimized. It is important that patients receive careful instruction in the use of pressurized (aerosol) inhalation (using a metered-dose inhaler) to obtain optimum benefit from their medication. Before use, the inhaler should be shaken well. After exhaling as completely as possible, the mouthpiece of the inhaler should be placed well into the mouth and the lips firmly closed around it. The patient should inhale deeply through the mouth while actuating the inhaler. After holding the breath for 10 seconds or as long as is comfortable, the mouthpiece should be removed and the patient should exhale slowly.

It is important to check that patients continue to use their inhalers correctly as inadequate technique may be mistaken for drug failure. Spacing devices provide a space between the inhaler and the mouth. They may be of benefit for patients such as the elderly, small children, and asthmatics who find inhalers difficult to use, or for those who have difficulty synchronizing their breathing with administration of the aerosol. A large-volume spacing device is also recommended for inhalation of high doses of corticosteroids to reduce oropharyngeal deposition, which can cause candidiasis. The use of metered-dose inhalers with spacers is less expensive and may be as effective as use of nebulizers, although drug delivery may be affected by choice of spacing device.

Breath-actuated devices, including dry powder inhalers, are also available.

Solutions for nebulization are available for use in acute severe asthma. They are administered over a period of 5–10 minutes from a nebulizer, usually driven by oxygen in a hospital setting.

Oral

The oral route is used when administration by inhalation is not possible.

Systemic adverse effects occur more frequently when a drug is given orally rather than by inhalation. Drugs given by mouth for the treatment of asthma include beta2-agonists, corticosteroids, leukotriene-receptor antagonists, and theophylline.

Parenteral

Drugs such as beta2-agonists, corticosteroids, and aminophylline may be given by injection in acute severe asthma when administration by nebulization is inadequate or inappropriate. If the patient is being treated in the community, urgent transfer to the hospital should be arranged.

Pregnancy

Poorly controlled asthma in pregnant women can have an adverse effect on the fetus, resulting in perinatal mortality, increased prematurity, and low birth weight. For this reason, using medications to obtain optimal control of asthma during

pregnancy is justified. Administration of drugs by inhalation during pregnancy has the advantage that plasma drug concentrations are not likely to be high enough to have an effect on the fetus. Acute exacerbations should be treated aggressively in order to avoid fetal hypoxia; if available, oxygen should be given immediately to maintain adequate oxygenation.

Breast-feeding

Inhaled drugs, oral prednisolone, and oral theophylline can be taken during breast-feeding.

Acute exacerbation of asthma

Severe asthma can be fatal and MUST be treated promptly and energetically. Acute severe asthma attacks require admission to the hospital, where resuscitation facilities are immediately available.

Severe asthma is characterized by persistent dyspnea (even at rest) that is poorly relieved by bronchodilators, exhaustion, a high pulse rate (usually more than 120/min), a high respiratory rate, and a very low peak expiratory flow. As asthma becomes more severe, wheezing may be absent. Patients should be given oxygen 40–60% (if available) (see *also* Section 1.1). Patients should also be given a beta2-agonist, **salbutamol** or terbutaline via a nebulizer, preferably driven by oxygen. In emergencies where a nebulizer is not available, salbutamol, 100 micrograms by aerosol inhalation, can be repeated 10–20 times, preferably

using a large-volume spacing device. If life-threatening features are present or the response to the beta2-agonist is poor, **ipratropium bromide** can be added to the nebulizer. Patients should also be given a corticosteroid; in adults, the recommended doses are prednisolone, 30–60 mg by mouth *or* hydrocortisone, 200 mg (preferably as sodium succinate) intravenously; and for children, prednisolone, 1–2 mg/kg by mouth (1–4 years, max. 20 mg; 5–15 years, max. 40 mg) or hydrocortisone, 100 mg (preferably as sodium succinate) intravenously. In case of vomiting, the parenteral route may be preferred for the first dose.

Most patients do not benefit from the addition of intravenous aminophylline or a parenteral beta2-agonist; both cause more adverse effects than nebulized beta2-agonists. Nevertheless, an occasional patient who has not been taking theophylline may benefit from a slow intravenous infusion of aminophylline.

The use of **epinephrine** (adrenaline) in asthma has generally been superseded by beta2-selective adrenoceptor agonists.

Treatment should **never** be delayed for investigations, patients should never be sedated and the possibility of pneumothorax should be considered. Patients who deteriorate further despite treatment may need intermittent positive pressure ventilation.

Chronic obstructive pulmonary disease

Decline in lung function in chronic obstructive pulmonary disease (COPD), chronic bronchitis, or emphysema, is reduced by cessation of smoking. Infection can complicate COPD and may be prevented by vaccination, for example, with the influenza vaccine.

A limited trial of a high-dose inhaled corticosteroid or an oral corticosteroid is recommended for patients with moderate airflow obstruction to ensure that asthma has not been overlooked. Chronic obstructive pulmonary disease may be helped by an inhaled short-acting beta2-agonist or an anticholinergic (antimuscarinic) bronchodilator (**ipratropium bromide**), used as required; when the airways obstruction is more severe, regular ipratropium bromide should be added. A long-acting beta2-adrenoceptor agonist, for example, salmeterol is added in those who remain symptomatic or have 2 or more exacerbations in a year; if these measures fail to improve symptoms, theophylline can be tried.

Moderate-to-severe disease may be treated with an inhaled corticosteroid and a long-acting beta2 adrenoceptor agonist; if no benefit is seen after 4 weeks, treatment should be discontinued. Exacerbations of COPD are treated with nebulized bronchodilators and oxygen (Section 1.1) if necessary; a short course of an oral corticosteroid should be given for increased breathlessness. Infection requires antibacterial treatment.

Long-term oxygen therapy prolongs survival in patients with severe COPD and hypoxemia.

Beta2-adrenoceptor agonists (beta2-adrenoceptor stimulants)

The adrenoreceptors in the bronchi are mainly of the beta2 type, and their stimulation causes bronchial muscles to relax. The beta2-adrenoceptor agonists (stimulants) include salbutamol, terbutaline, and tulobuterol. When salbutamol is given by inhalation, at doses in the range of 100–200 micrograms, the effect can last as long as 4 hours thus making it suitable for both the treatment and prevention of asthma. Salbutamol can also be taken orally in a dose of 2–4 mg up to 4 times daily, but is less effective and causes more adverse effects. It can also be given by injection for severe bronchospasm.

Adverse effects

Cardiovascular adverse effects (arrhythmias, palpitations, and tachycardia) may occur with salbutamol, but are generally infrequent with inhaled preparations.

Hypokalemia may also result from beta2-adrenoceptor agonist therapy.

Particular caution is required in severe asthma because this effect may be potentiated by concomitant treatment with xanthines (for example, theophylline), corticosteroids, or diuretics and by hypoxia. Plasma potassium concentrations should be monitored in severe asthma.

Xanthines

Xanthines include theophylline and aminophylline; they relax bronchial smooth muscle (relieving bronchospasm) and also stimulate respiration. Theophylline has a narrow margin between therapeutic and toxic effects. At therapeutic doses, some patients experience nausea and diarrhea and when plasma concentrations exceed the recommended range of 10–20 mg/L (55–110 micromol/L) arrhythmias and convulsions, which may be fatal, can occur. Monitoring of plasma concentrations is therefore recommended. Theophylline is sometimes used to treat asthma and stable COPD.

Theophylline is given by injection as aminophylline (a mixture of theophylline and ethylenediamine), which is 20 times more soluble in water than theophylline alone. It is used rarely by slow intravenous injection for the management of severe asthma attacks.

Corticosteroids

Inhaled corticosteroids

Inhaled corticosteroids, such as **beclometasone**, are the most effective anti-inflammatory medications for the treatment of asthma. They are recommended for the long-term control of asthma in patients using a beta2-adrenoceptor agonist more than once a week over a 3-month period and some episodes of

asthma affect sleep and activity. Regular use of inhaled corticosteroids reduces the risk of exacerbations of asthma.

Corticosteroids must be used regularly to obtain maximum benefit. Symptom control is usually effective after 3–7 days of treatment. Long-term high-dose regimens of inhaled corticosteroids are preferred for the treatment of severe persistent asthma because they reduce the need for the long-term use of oral corticosteroids and also have fewer systemic adverse effects.

Local adverse effects from inhaled corticosteroids include oropharyngeal candidiasis, dysphonia, and occasional coughing from upper airway irritation. The use of spacing devices reduces oropharyngeal deposition and thus reduces the incidence of candidiasis; rinsing the mouth with water or brushing teeth after using an inhaled corticosteroid may also be helpful. Coughing may be reduced by the use of a beta₂-agonist before using a corticosteroid inhaler. The risk for systemic effects of inhaled corticosteroids is small and is dependent on the dose and potency of the corticosteroid, as well as its bioavailability and the plasma half-life of its systemically absorbed fraction. Systemic effects are rare and include skin thinning and easy bruising, a small increased risk of glaucoma and cataracts, adrenal suppression, decrease of bone metabolism, and growth retardation in children.

Systemic corticosteroids

Oral **corticosteroids** (Sections 3 and 18.1) may be used as “maximum therapy” to achieve control of a patient’s asthma. This may be useful either when initiating long-term therapy for a patient with uncontrolled asthma or as a short “rescue” course at any stage for acute exacerbation.

Long-term oral corticosteroid therapy may be required to control severe persistent asthma, but its use is limited by the risk of significant adverse effects. In these cases, high-dose inhaled corticosteroids should be continued so that oral requirements are reduced to a minimum. Oral doses should be given as a single dose in the morning to reduce the disturbance to the circadian cortisol secretion. Dosage should always be adjusted to the lowest dose that controls symptoms.

Sodium cromoglicate

Sodium cromoglicate may be helpful in asthma with an allergic basis, but it is difficult to predict who might benefit. In adults, prophylaxis with sodium cromoglicate is generally less effective than prophylaxis with inhaled corticosteroids. Sodium cromoglicate is of value in the prevention of exercise-induced asthma, a single dose being inhaled 30 minutes beforehand; however, exercise-induced asthma may indicate poor disease control and should prompt assessment of the patient. Sodium cromoglicate is of **NO VALUE for the treatment of acute attacks of asthma.**

Anticholinergic (antimuscarinic) bronchodilators

Ipratropium bromide can provide short-term relief in chronic asthma, but short-acting beta₂-agonists work more quickly and are usually preferred; ipratropium bromide is also added to standard treatment regimens where asthma is life-threatening or when an acute attack does not respond to standard therapy. Ipratropium bromide is also used as a bronchodilator in COPD.

Leukotriene receptor antagonists

The leukotriene receptor antagonists, including montelukast, block the effects of cysteinyl leukotrienes in the airways. They are effective in asthma when used alone or with an inhaled corticosteroid; they may be of benefit in exercise-induced asthma and in those with concomitant rhinitis but are less effective in those with severe asthma who are also receiving high doses of other drugs. Very rarely Churg-Strauss syndrome has occurred in association with the use of leukotriene receptor antagonists; this reaction has often followed the reduction or withdrawal of oral corticosteroid therapy. Prescribers and patients should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.

- **Aminophylline**

Aminophylline is a stable mixture or combination of theophylline and ethylenediamine; they relax bronchial smooth muscle (relieving bronchospasm) and also stimulate respiration.

- **Dosage form**

- Tablet: 100 mg
- Injection solution: 25 mg/ml in 10 ml ampoule

- **Uses**

- Reversible airways obstruction, severe acute asthma

- **Contraindications**

- Porphyria
- Hypersensitivity to ethylenediamine

- **Precautions**

- Cardiac disease
- Hypertension
- Hyperthyroidism
- Peptic ulcer
- Epilepsy
- Elderly

- Fever
- Dose adjustment may be necessary if smoking started or stopped during treatment
- Hepatic impairment: Appendix E
- Pregnancy: Appendix B
- Breast-feeding: Appendix C
- **Adverse effects**
 - Nausea, vomiting, gastric irritation, diarrhea
 - Palpitation, tachycardia
 - Anxiety, dizziness, tremor, headache, CNS stimulation, insomnia, and convulsions
 - Also allergy to ethylenediamine can cause urticaria, erythema, and exfoliative dermatitis
 - Hypotension, arrhythmias, and convulsions, especially if given rapidly by intravenous injection
- **Dose**

Severe acute asthma or acute exacerbation of chronic obstructive pulmonary disease in patients not previously treated with theophylline

- **ADULT:** By slow intravenous injection over at least 20 minutes (with close monitoring), 250–500 mg (5 mg/kg), then by intravenous infusion (with close monitoring), 500–700 micrograms/kg/hour
- **ELDERLY:** 300 micrograms/kg/hour;
- **CHILD** under 12 years: 5 mg/kg, then by slow intravenous infusion (with close monitoring) 1 mg/kg/hour

In the management of acute or chronic bronchospasm, orally

- **ADULT:** 100–300 mg three or four times daily after food.

Note: Patients taking oral theophylline or aminophylline should not normally receive a loading dose of intravenous aminophylline; if possible, plasma theophylline concentration should be measured in all patients receiving intravenous aminophylline.

- **Beclometasone**

Beclometasone dipropionate is a representative corticosteroid. Various medicines can serve as alternatives.

- **Dosage form**

- Inhalation (aerosol): 50 micrograms per dose (dipropionate) and 250 micrograms (dipropionate) per dose
- Nebulizer solution: 800 microgram/2 ml

- **Uses**

- Chronic asthma not controlled by short-acting beta2-adrenoceptor agonists

- **Precautions**

- See note above.
- Active or quiescent tuberculosis
- Systemic therapy may be required during periods of stress or when airway obstruction or mucus prevent drug access to smaller airways.
- Not for relief of acute symptoms
- Monitor height of children receiving prolonged treatment.
- If growth is slowed, review therapy.

- **Dose**

Chronic asthma, by aerosol inhalation (standard-dose inhaler)

- **ADULT:** 200 micrograms twice daily or 100 micrograms 3–4 times daily (in more severe cases, initially 600–800 micrograms daily)
- **CHILD:** 50–100 micrograms 2–4 times daily or 100–200 micrograms twice daily

Chronic asthma, by aerosol inhalation (high-dose inhaler)

- **ADULT:** 500 micrograms twice daily or 250 micrograms 4 times daily; if necessary may be increased to 500 micrograms 4 times daily
 - **CHILD:** Not recommended
- **Adverse effects**
- Oropharyngeal candidiasis, cough, and dysphonia (usually only with high doses)
 - Adrenal suppression, growth retardation in children and adolescents, impaired bone metabolism, glaucoma, and cataract (with high doses, but less frequent than with systemic corticosteroids)
 - Paradoxical bronchospasm (requires discontinuation and alternative therapy but if mild, may be prevented by inhalation of beta2-adrenoceptor agonist or by transfer from aerosol to powder inhalation)
 - Rarely urticaria, rash, and angioedema
 - Very rarely anxiety, sleep disorders, and behavioral changes

Candidiasis: Candidiasis can be reduced by the use of a spacing device (see introductory note above); rinsing the mouth with water after inhalation may also help to prevent candidiasis.

- **Epinephrine (adrenaline)**

- **Dosage form**

- Injection: 0.1% in 1 ml ampoule
 - See Section 3.

- **Salbutamol**

Salbutamol is a representative beta2-adrenoceptor agonist. Various drugs can serve as alternatives.

- **Dosage form**

- Tablets: 2 mg and 4 mg
 - Syrup: 2 mg/5 ml
 - Injection: 0.05 mg/ml and 0.5 mg/ml
 - Nebulizer solution: 5 mg/ml
 - Inhalation (aerosol): 0.1 mg per dose

- **Uses**

- Prophylaxis and treatment of asthma

- **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;
see *also* introductory note above and Appendix B)

- Breast-feeding: Appendix C
- Diabetes mellitus, especially intravenous administration
(ketoacidosis reported; monitor blood glucose)
- **Interactions:** Appendix A

○ **Dose**

Chronic asthma (when inhalation is ineffective), by mouth

- **ADULT:** 2–4 mg, 3–4 times daily; in some patients up to a maximum of 8 mg 3–4 times daily
- **CHILD** under 2 years: 100 micrograms/kg 4 times daily
- **CHILD** 2–6 years: 1–2 mg 3–4 times daily
- **CHILD** 6–12 years: 2 mg 3–4 times daily

Severe acute bronchospasm, by slow intravenous injection

- **ADULT:** 250 micrograms, repeated if necessary

Relief of acute bronchospasm, by aerosol inhalation

- **ADULT:** 100–200 micrograms (1–2 puffs)
- **CHILD:** 100 micrograms (1 puff) increased to 200 micrograms 2 puffs) if necessary

Relief of acute bronchospasm, by intramuscular or subcutaneous injection

- **ADULT:** 500 micrograms repeated every 4 hours if necessary

Prophylaxis of exercise-induced bronchospasm, by aerosol inhalation

- **ADULT:** 200 micrograms (2 puffs)
- **CHILD:** 100 micrograms (1 puff) increased to 200 micrograms (2 puffs) if required

Chronic asthma (as adjunct in stepped treatment), by aerosol inhalation

- **ADULT:** 100–200 micrograms (1–2 puffs) up to 3–4 times daily
- **CHILD:** 100 micrograms (1 puff) 3–4 times daily, increased to 200 micrograms (2 puffs) 3–4 times daily if necessary

Severe acute asthma, chronic bronchospasm (unresponsive to conventional treatment), by inhalation of nebulized solution

- **ADULT** and **CHILD** over 18 months: 2.5 mg repeated up to 4 times daily; may be increased to 5 mg if necessary (medical assessment should be considered since alternative therapy may be indicated)
- **CHILD** under 18 months: Clinical efficacy uncertain (transient hypoxemia may occur—consider oxygen supplementation)

- **Adverse effects**
 - Hypokalemia after high doses
 - Arrhythmias, tachycardia, palpitations, fine tremor (usually hands), muscle cramps, headache, insomnia, behavioral disturbances in children
 - Paradoxical bronchospasm, urticaria, and angioedema also reported
 - Slight pain on intramuscular injection

25.2 OTHER MEDICINES ACTING ON THE RESPIRATORY TRACT

- **Naphazoline**

- **Dosage form**
 - Nasal drop: 0.05% in 10 ml bottle
- **Uses and administration**
 - Naphazoline as hydrochloride or nitrate is used for the symptomatic relief of nasal congestion
 - **ADULT:** Naphazoline may be applied topically as nasal drops or spray usually up to once every 6 hours

- **CHILD:** 2 or 3 times daily, in children aged 7 years and over for the symptomatic relief of nasal congestion
- **Precautions**
 - **Interactions:** Since naphazoline is absorbed through the nasal mucosa, interactions may follow topical application; see Appendix A.
- **Adverse effects**
 - Transient irritation
 - Rebound congestion
 - Nausea, headache, and dizziness
 - Overdosage or accidental oral use may cause central nervous system (CNS) depression with marked reduction of body temperature and bradycardia, sweating, drowsiness, and coma, particularly in children.
 - Use in the eye may liberate pigment granules from the iris, especially when given in high doses to elderly patients.
 - Hypertension may be followed by rebound hypotension.

SECTION 26: Solutions correcting water, electrolyte, and acid-base disturbances

LML strengths and dosage forms are marked in *italic* with an asterisk.

26.1 ORAL SOLUTION

ORS solution

See Section 17.5.1.

- **Oral rehydration salts for malnourished child (ReSoMal)**
 - **Composition**
 - Glucose: 125 mmol/L, sodium: 45 mmol/L, potassium: 40 mmol/L, chloride: 70 mmol/L, citrate: 7 mmol/L, magnesium: 3 mmol/L, zinc: 0.3 mmol/L, copper: 0.045 mmol/L, osmolality: 300 mmol/L
 - **Dosage form**
 - Oral ingestion powder: 42 g sachet
 - **Uses**
 - Management of dehydration in severely malnourished children
 - Dedicated only for therapeutic feeding units

- **Contraindication**
 - Not to be used out of therapeutic feeding units
- **Precaution**
 - Acute malnourished patients during diarrhea for self-use
- **Dose**
 - Dissolve the powder in 1 liter cooled water and use within 24 hours.
 - The dosage may vary according to patients condition from 5–10 ml/kg for 2 hours, followed by 5 mg/kg for 10 hours.
- **Adverse effects**
 - Increase of respiratory and cardiac pulse rate
 - Precipitation of edema in edematous patients (discontinue immediately and seek proper measure)
- **Potassium chloride**
 - **Dosage form**
 - Powder for solution
 - Compensation for potassium loss is necessary in patients taking digoxin (Sections 12.2 and 12.4) or other anti-arrhythmic drugs where potassium depletion may induce arrhythmias.

- It is also necessary in patients with secondary hyperaldosteronism (renal artery stenosis, liver cirrhosis, the nephrotic syndrome, severe heart failure) and those with excessive loss of potassium in the feces (chronic diarrhea associated with intestinal malabsorption or laxative abuse).
- Measures to compensate for potassium loss may also be required in the elderly since they often consumer inadequate amounts in their diet (exercise caution in renal insufficiency; see below).
- Measures may also be required during long-term administration of drugs known to induce potassium loss (for example, corticosteroids and thiazide and loop diuretics).
- However, potassium supplements are seldom required with the small doses of diuretics given to treat hypertension.
- Potassium-sparing diuretics (rather than potassium supplements) are recommended for prevention of hypokalemia due to diuretics such as furosemide or the thiazides when these are given to eliminate edema (see Section 16).
- For the prevention of hypokalemia, doses of potassium chloride 2–4 g (approximately 25–50 mmol) daily by mouth are suitable in most patients consuming a normal diet.
- Smaller doses must be used in renal insufficiency (common in the elderly), otherwise there is a danger of hyperkalemia.

- Larger doses may be required in established potassium depletion, the quantity depending on the severity of any continuing potassium loss (monitoring of plasma potassium and specialist advice are required).
 - Potassium depletion is frequently associated with metabolic alkalosis and chloride depletion and these disorders require correction.
- **Uses**
 - Prevention and treatment of hypokalemia
 - Electrolyte imbalance (Section 26.2)
- **Contraindications**
 - Severe renal impairment
 - Plasma potassium concentration above 5 mmol/L
- **Precautions**
 - Elderly
 - Mild-to-moderate renal impairment (close monitoring required):
Appendix D
 - History of peptic ulcer
 - **Interactions:** Appendix A

Important: Extra caution is required when given with drugs liable to raise plasma potassium concentrations, such as potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, or ciclosporin.

- **Dose**

Prevention of hypokalemia, by mouth

- **ADULT:** 20–50 mmol daily after meals (possibly lower doses in the elderly)

Potassium depletion, by mouth

- **ADULT:** 40–100 mmol daily in divided doses after meals; adjust dose according to severity of deficiency and any continuing loss of potassium

- **Reconstitution and administration**

- According to manufacturer's directions

- **Adverse effects**

- Nausea and vomiting, gastrointestinal irritation

26.2 PARENTERAL SOLUTION

Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses, when the patient is nauseated or vomiting, or otherwise unable to take adequate amounts by mouth.

The nature and severity of the electrolyte imbalance must be assessed based on the history and clinical and biochemical examination of each individual. Sodium, potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination, and with or without disturbances of the acid–base balance.

Isotonic solutions may be infused safely into a peripheral vein. More concentrated solutions, for example, 20% glucose, are best given through an indwelling catheter positioned in a large vein.

Sodium chloride in isotonic solution provides the most important extracellular ions in near-physiological concentrations and is indicated in *sodium depletion*, which may arise from conditions such as gastroenteritis, diabetic ketoacidosis, ileus, and ascites. In a severe deficit—of 4–8 L to 2–3 L of isotonic sodium chloride may be given over 2–3 hours; thereafter, infusion can usually be at a slower rate. Excessive administration should be avoided; the jugular venous pressure should be assessed; the bases of the lungs should be examined for

crepitations, and in the elderly or seriously ill patients it is often helpful to monitor the right atrial (central) venous pressure.

Chronic hyponatremia should ideally be managed by fluid restriction. However, if sodium chloride is required, the deficit should be corrected slowly to avoid risk of osmotic demyelination syndrome; the rise in plasma sodium concentration should not exceed 10 mmol/L in 24 hours. In severe hyponatremia, intravenous infusion of sodium chloride, 1.8%, may be used with caution.

The more physiologically appropriate **compound solution of sodium lactate** can be used instead of isotonic sodium chloride solution during surgery or in the initial management of the injured or wounded.

Sodium chloride and glucose solutions are indicated when there is *combined water and sodium depletion*. A 1:1 mixture of isotonic sodium chloride and 5% glucose allows some of the water (free of sodium) to enter the body cells that suffer most from dehydration, while the sodium salt (with a volume of water determined by the normal plasma sodium ion) remains extracellular. Combined sodium, potassium, chloride, and water depletion may occur—for example, with severe diarrhea or persistent vomiting; replacement is carried out with sodium chloride intravenous infusion, 0.9%, and glucose intravenous infusion, 5%, with potassium as appropriate.

Glucose solution, 5%, is mainly used to replace *water deficits* and should be given alone when there is no significant loss of electrolytes. The average water requirement in a healthy adult is 1.5–2.5 L daily; this is needed to balance unavoidable losses of water through the skin and lungs and to provide sufficient for urinary excretion. Water depletion (dehydration) tends to occur when these losses are not matched by a comparable intake as, for example, may occur in coma or dysphagia or in the elderly or apathetic who may not drink water in a sufficient amount on their own initiative.

Excessive loss of water without loss of electrolytes is uncommon, occurring in fevers, hyperthyroidism, and in rare water-losing renal states such as diabetes insipidus or hypercalcemia. The volume of glucose solution needed to replace deficits varies with the severity of the disorder, but usually lies within the range of 2–6 L.

Glucose solutions are also given in regimens with calcium, bicarbonate, and insulin for the emergency treatment of *hyperkalemia*. They are also given, after correction of hyperglycemia, during treatment of *diabetic ketoacidosis*, when they must be accompanied by continuous insulin infusion.

If glucose or sugar cannot be given orally to treat *hypoglycemia*, glucose, 50%, may be given intravenously using a large vein and a large-gauge needle; this concentration is very irritant on extravasation; it is also viscous and therefore

especially difficult to administer. Larger volumes of less concentrated glucose solutions (10% or 20%) can be used as alternatives and are less irritant.

Sodium hydrogen carbonate (sodium bicarbonate) is used to control severe *metabolic acidosis* (as in renal failure). Since this condition is usually attended by sodium depletion, it is reasonable to correct this first by the administration of isotonic sodium chloride intravenous infusion, provided the kidneys are not primarily affected and the degree of acidosis is not so severe as to impair renal function. In these circumstances, isotonic sodium chloride alone is usually effective, as it restores the ability of the kidneys to generate bicarbonate. In renal acidosis or in severe metabolic acidosis of any origin (for example, blood pH < 7.1), sodium hydrogen carbonate, 1.4%, may be infused with isotonic sodium chloride when the acidosis remains unresponsive to correction of anoxia or fluid depletion; a total volume of up to 6 L (4 L of sodium chloride and 2 L of sodium hydrogen carbonate) may be necessary in an adult. In severe shock—for example due to cardiac arrest—metabolic acidosis may develop without sodium depletion; in these circumstances, sodium hydrogen carbonate is best given in a small volume of hypertonic solution (for example, 50 ml of 8.4% solution intravenously); plasma pH should be monitored. Sodium hydrogen carbonate is also used in the emergency management of hyperkalemia.

Intravenous **potassium chloride** in sodium chloride solution is the initial treatment for the correction of *severe hypokalemia* when sufficient potassium

cannot be taken by mouth. Potassium chloride concentrate may be added to sodium chloride solution, 0.9%, for infusion, thoroughly mixed, and given slowly over 2–3 hours under specialist advice and with ECG monitoring in difficult cases. Repeated measurements of plasma potassium are necessary to determine whether further infusions are required and to avoid the development of hyperkalemia, which is especially likely to occur in renal impairment.

Initial intravenous potassium replacement therapy should **NOT** involve glucose solutions because glucose may cause a further decrease in the plasma-potassium concentration.

- **Glucose**

- **Dosage form**

- Injectable solution: 5% and 10% in 500 or 1000 ml bottle (isotonic); 25% in 10 ml ampoule and 50% (hypertonic) injection solution
 - Oral powder

- **Uses**

- Fluid replacement without significant electrolyte deficit
 - Treatment of hypoglycemia

- **Precautions**

- Diabetes mellitus (may require additional insulin)

- **Dose**

Fluid replacement, by intravenous infusion

- **ADULT** and **CHILD**: Determined on the basis of clinical and, whenever possible, electrolyte monitoring (see *also* introductory note above)

Treatment of hypoglycemia, by intravenous infusion of 50% glucose solution into a large vein

- **ADULT**: 25 ml (see *also* introductory note above)

- **Adverse effects**

- Glucose injections, especially if hypertonic, have a low pH and may cause venous irritation and thrombophlebitis
- Fluid and electrolyte disturbances
- Edema or water intoxication (on prolonged administration or rapid infusion of large volumes of isotonic solutions)
- Hyperglycemia (on prolonged administration of hypertonic solutions)

- **Glucose with sodium chloride**

- **Dosage form**

- Injectable solution: Glucose 4% + sodium chloride 0.18% in 500 ml and 1,000 ml bottles; glucose 5% + sodium chloride 0.9% in 500 ml and 1,000 ml bottles

- **Uses**

- Fluid and electrolyte replacement

- **Precautions**

- Restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary edema, and toxemia during pregnancy

- **Dose**

Fluid replacement, by intravenous infusion

- **ADULT** and **CHILD**: Determined on the basis of clinical and, whenever possible, electrolyte monitoring (see *also* introductory note above)

- **Adverse effects**

- Administration of large doses may give rise to edema.

- **Potassium chloride**

- **Dosage form**

- Injection solution: 7.5%, 11.2%, and 15% in 20 ml ampoules

- **Uses**

- Electrolyte imbalance
 - Prevention and treatment of hypokalemia (Section 26.1)

- **Precautions**

- For intravenous infusion, the concentration of solution should not usually exceed 3.2 g (43 mmol)/L; administer under specialist advice and with plasma potassium and ECG monitoring.
 - Renal impairment: Appendix D
 - **Interactions:** Appendix A

- **Dose**

- Electrolyte imbalance, by slow intravenous infusion*

- **ADULT** and **CHILD:** Depending on the deficit or the daily maintenance requirements (see *also* introductory note above)

- **Dilution and administration**

- Must be diluted and thoroughly mixed before use and administered according to manufacturer's directions

- **Adverse effects**

- Cardiac toxicity on rapid infusion

- **Ringer's lactate / sodium lactate**

The sodium lactate composite solution is one of the intravenous electrolyte solutions that is used as an alternative to other solutions.

- **Dosage form**

- Injectable solution: Sodium chloride, 0.6%; sodium lactate, 0.32%; potassium chloride, 0.04%; calcium chloride, 0.027% (contains 131 mmol sodium, 5 mmol potassium, 2 mmol calcium, 29 mmol bicarbonate [as lactate], and 111 mmol chlorine per L)

- **Uses**

- Correcting fluid and electrolyte imbalance during and after surgery and hypovolemic shock
- Sodium lactate compound solution is a proper physiologic solution that can be administered during surgery and for the treatment of injured and traumatized patients as a replacement of isotonic sodium chloride solution.

- **Contraindications**

- Metabolic alkalosis and respiratory alkalosis, hypocalcemia, hypochlorhydria (decreased secretion of hydrochloric acid)

- **Precautions**

- Limit using during renal function disorders, heart failure, hypertension, peripheral edema, alveolar edema, and pregnancy toxemia

- **Dose**

Fluid and electrolyte replacement or hypovolemic shock, by intravenous infusion

- **ADULT** and **CHILD**: Determined on the basis of clinical and, whenever possible, electrolyte monitoring

- **Adverse effects**

- Excessive administration may cause metabolic alkalosis.
- Administration of large doses may give rise to edema.

- **Sodium chloride**

- **Dosage form**

- Injectable solution: 0.9% isotonic (equivalent to Na⁺154 mmol/L, Cl⁻ 154 mmol/L) in 500 ml and 1,000 ml bottles

- **Uses**

- Electrolyte and fluid replacement

- **Precautions**

- Restrict intake in impaired renal function: Appendix D
 - Cardiac failure, hypertension, peripheral and pulmonary edema, and toxemia during pregnancy

- **Dose**

Fluid and electrolyte replacement, by intravenous infusion

- **ADULT** and **CHILD**: Determined on the basis of clinical and, whenever possible, electrolyte monitoring (see *also* introductory note above)

- **Adverse effects**

- Administration of large doses may give rise to sodium accumulation and edema

- **Sodium hydrogen carbonate / sodium bicarbonate**

- **Dosage form**

- Injectable solution: 1.4% and 7.5% in 20 ml vial and 8.4% in 10 ml vial; also as powder

- **Use**

- Metabolic acidosis

- **Contraindications**

- Metabolic or respiratory alkalosis, hypocalcemia, hypochlorhydria

- **Precautions**

- Restrict intake in impaired renal function: Appendix D
 - Cardiac failure, hypertension, peripheral and pulmonary edema, and toxemia during pregnancy
 - Monitor electrolytes and acid–base status
 - **Interactions:** Appendix A

- **Dose**

Metabolic acidosis, by slow intravenous injection of a strong solution (up to 8.4%) or by continuous intravenous infusion of a weaker solution (usually 1.4%)

- **ADULT** and **CHILD**: An amount appropriate to the body base deficit (see note above)
- **Adverse effects**
 - Excessive administration may cause hypokalemia and metabolic alkalosis, especially in renal impairment.
 - Large doses may give rise to sodium accumulation and edema.

26.3 MISCELLANEOUS

- **Water for injection**
 - **Dosage form**
 - 5 ml and 10 ml ampoules
 - **Uses**
 - In preparations intended for parenteral administration and in other sterile preparations

SECTION 27: Vitamins and minerals

LML strengths and dosage forms are marked in *italic* with an asterisk.

Vitamins

Vitamins are used for the prevention and treatment of specific deficiency states or when the diet is known to be inadequate. It has often been suggested, but never convincingly proved, that sub-clinical vitamin deficiencies cause much chronic ill health and liability to infections. This has led to enormous consumption of vitamin preparations, which may have no more than placebo value. Most vitamins are comparatively non-toxic but prolonged administration of high doses of retinol (vitamin A), ergocalciferol (vitamin D2), and pyridoxine (vitamin B6) may have severe adverse effects.

Retinol (vitamin A) is a fat-soluble substance stored in body organs, principally the liver. Periodic high-dose supplementation is intended to protect against vitamin A deficiency, which is associated with ocular defects, particularly xerophthalmia (including night blindness, which may progress to severe eye lesions and blindness), and an increased susceptibility to infections, particularly measles and diarrhea. Universal vitamin A distribution involves the periodic administration of supplemental doses to all preschool-aged children, with priority given to the age group of 6 months–3 years, or regions at greatest risk of clinical and sub-clinical deficiencies. In addition, all mothers in high-risk regions should

receive a high dose of vitamin A within 8 weeks of delivery. Since vitamin A is associated with a teratogenic effect, it should be given in smaller doses (no more than 10,000 IU/day) to all women of childbearing age. Vitamin A is also used in the treatment of active xerophthalmia. Doses of vitamin A should be administered orally immediately upon diagnosis of xerophthalmia, and thereafter patients with acute corneal lesions should be referred to a hospital on an emergency basis. In women of childbearing age, there is a need to balance the possible teratogenic effects of vitamin A should they be pregnant with the serious consequences of xerophthalmia. Where there are severe signs of xerophthalmia, high-dose treatment (that is, in patients over 1 year) should be given. When less severe symptoms are present (for example, night blindness), a much lower dose is recommended. Vitamin A therapy should also be given during epidemics of measles to reduce the risk of complications.

Vitamin B is composed of widely differing substances, which are, for convenience, classed as “vitamin B complex.” **Thiamine** (vitamin B1) is used orally for deficiency due to inadequate dietary intake. Severe deficiency may result in beri-beri. Chronic dry beri-beri is characterized by peripheral neuropathy, muscle wasting and weakness, and paralysis; wet beri-beri is characterized by cardiac failure and edema. Wernicke-Korsakoff syndrome (demyelination of the central nervous system) may develop in severe deficiency. Thiamine is given by intravenous injection in doses of up to 300 mg daily (parenteral preparations may contain several B group vitamins) as initial

treatment in severe deficiency states. As potentially severe allergic reactions may occur during, or shortly after, parenteral administration, intravenous injections should be administered slowly (over 10 minutes) and should be used only if parenteral treatment is essential. Facilities for resuscitation should be immediately available.

Riboflavin (vitamin B2) deficiency may result from reduced dietary intake or reduced absorption due to liver disease, alcoholism, chronic infection, or probenecid therapy. It may also occur in association with other deficiency states such as pellagra.

Pyridoxine (vitamin B6) deficiency is rare as the vitamin is widely distributed in foods, but deficiency may occur during isoniazid therapy and is characterized by peripheral neuritis. High doses are given in some metabolic disorders, such as hyperoxaluria, and it is also used in sideroblastic anemia. Pyridoxine and thiamine also have a role in status epilepticus (see Section 5).

Nicotinic acid inhibits the synthesis of cholesterol and triglyceride and is used in some hyperlipidemias. Nicotinic acid and **nicotinamide** are used to prevent and treat nicotinic acid deficiency (pellagra). Nicotinamide is generally preferred, as it does not cause vasodilation. Hydroxocobalamin is the form of vitamin B12 used to treat vitamin B12 deficiency due to dietary deficiency or malabsorption (see Section 10.1).

Folic acid is essential for the synthesis of DNA and certain proteins. Deficiency of folic acid or vitamin B12 is associated with megaloblastic anemia. Folic acid should not be used in undiagnosed megaloblastic anemia unless vitamin B12 is administered concurrently; otherwise, neuropathy may be precipitated.

Supplementation with folic acid, 400 micrograms daily, is recommended for women of childbearing potential in order to reduce the risk of serious neural tube defects in their offspring (see Section 10.1).

Ascorbic acid (vitamin C) is used for the prevention and treatment of scurvy.

Claims that ascorbic acid is of value in the treatment of common colds are unsubstantiated.

The term vitamin D covers a range of compounds, including **ergocalciferol** (vitamin D2) and **colecalciferol** (vitamin D3). These 2 compounds are equipotent and either can be used to prevent and treat rickets. Simple deficiency of vitamin D occurs in those who have an inadequate dietary intake or who fail to produce enough colecalciferol (vitamin D3) in their skin from its precursor, 7-dehydrocholesterol, in response to exposure to ultraviolet light. Children with dark skin must continue vitamin D prophylaxis for up to 24 months because of their inability to produce enough vitamin D3 in their skin. Dark skin, which has a high melanin content, must be exposed to daylight longer than light skin in order to obtain the same synthesis of vitamin D3. Vitamin D is also used in deficiency

states caused by intestinal malabsorption or chronic liver disease and for the hypocalcemia that is associated with hypoparathyroidism.

Phytomenadione (vitamin K), which is associated with phytomenadione, is necessary for the production of blood clotting factors (see Section 10.2).

Minerals

For the use of iron preparations in the treatment of anemia, see Section 10.1.

- **Calcium gluconate**

Calcium gluconate is a complementary list medicine.

Calcium supplements, in the form of calcium gluconate, are usually required only when dietary calcium intake is inadequate. This dietary requirement varies with age and is relatively greater in childhood and during pregnancy and lactation (due to an increased demand), and in old age (due to impaired absorption). In osteoporosis, a calcium intake that is double the recommended daily amount reduces the rate of bone loss. In hypocalcemic tetany, calcium gluconate must be given parenterally but plasma calcium must be monitored. Calcium gluconate is also used in cardiac resuscitation.

- **Dosage form**

- Injection: 10% in 10 ml ampoule

- **Uses**

- Hypocalcemic tetany

- **Contraindications**

- Conditions associated with hypercalcemia and hypercalciuria (for example, some forms of malignant disease)

- **Precautions**

- Monitor plasma calcium concentration
- Renal impairment: Appendix D
- Sarcoidosis
- History of nephrolithiasis
- **Interactions:** Appendix A

- **Dose**

Hypocalcemic tetany, by slow intravenous injection

- **ADULT:** 1 g (2.2 mmol) followed by about 4 g (8.8 mmol) daily *by continuous intravenous infusion*

- **Dilution and administration**

- According to manufacturer's directions

- **Adverse effects**

- Gastrointestinal disturbances
- Bradycardia, arrhythmia
- Injection-site reactions

- Peripheral vasodilation
- Fall in blood pressure

- **Colecalciferol / vitamin D3**

- **Dosage form**

- Injectable solution: 600,000 IU/ml

- **Uses**

- Prevention and treatment of vitamin D deficiency
 - Treatment of vitamin D deficiency caused by malabsorption or chronic liver diseases
 - Hypocalcemia due to hypoparathyroidism

- **Contraindication**

- Hypercalcemia, calcification metastatic

- **Precaution**

- Appropriate dosage is recommended for newborn infants.
 - Monitor plasma calcium levels in 1-week intervals in patients receiving high doses or patients suffering from kidney functional disorders
 - Nausea and vomiting may indicate overdose and hypercalcemia.
 - Pregnancy: Appendix B
 - Breast-feeding: Appendix C
 - **Interaction:** Appendix A

- **Dose**
 - For the prevention of vitamin D deficiency; 100,000 units every 6 months for children and 200,000 units every 6 months for adults in a single dose
- **Adverse effects**
 - Anorexia, lethargy, nausea, vomiting, diarrhea, weight loss, polyuria, sweating, headache, thirst, dizziness; high plasma, and urine calcium and phosphate levels
 - Tissue calcification can occur in case of taking continuous dose of 1.25 mg for several months
- **Folic acid**
 - **Dosage form**
 - Tablet: 1 mg and 5 mg
 - **Uses**
 - Treatment of folate-deficiency megaloblastic anemia
 - Prevention of neural tube defects in pregnancy
 - **Contraindications**

- Should never be given without vitamin B12 in undiagnosed megaloblastic anemia or other vitamin B12 deficiency states because of the risk of precipitating sub-acute combined degeneration of the spinal cord
- Folate-dependent malignant disease
- **Precautions**
 - Women receiving anti-epileptic therapy (counseling is needed before starting folic acid; see *also* note above)
 - ***Interactions:*** Appendix A
- **Dose**

Treatment of folate-deficiency, megaloblastic anemia, by mouth

- **ADULT:** 5 mg daily for 4 months (in pregnancy continued to term); up to 15 mg daily may be necessary in malabsorption state

Prevention of first occurrence of neural tube defects, by mouth

- **ADULT:** 400–500 micrograms daily before conception and during the first 12 weeks of pregnancy

Prevention of recurrence of neural tube defects, by mouth

- **ADULT:** 5 mg daily (reduced to 4 mg daily, if suitable preparation available) from at least 4 weeks before conception until 12th week of pregnancy

- **Iodine**

Iodine is among the body's essential trace elements. The recommended intake of iodine for adults is 150 micrograms daily (200 micrograms daily in pregnant and lactating women); in children, the recommended intake of iodine is 50 micrograms daily for infants under 1 year, 90 micrograms daily for children aged 2—6 years, and 120 micrograms daily for children aged 7—12 years. Deficiency causes endemic goiter and results in endemic cretinism (characterized by deaf-mutism, intellectual deficit, spasticity, and sometimes hypothyroidism), impaired mental function in children and adults, and an increased incidence of stillbirths and perinatal and infant mortality. Iodine and iodides may suppress neonatal thyroid function, and in general, iodine compounds should be avoided in pregnancy. Where it is essential to prevent neonatal goiter and cretinism, iodine should not be withheld from pregnant women. Control of iodine deficiency largely depends upon salt iodization (with potassium iodide or potassium iodate) and dietary diversification. In areas where iodine deficiency disorders are moderate to severe, iodized oil, given either before or at any stage of pregnancy, is found to be beneficial.

- **Dosage form**

- Capsule: 200 mg
- Iodized oil: 480 mg iodine/ml in 0.5 ml ampoule (240 mg iodine)
and oral preparations containing 540 mg/ml in 0.57 ml bottle (308 mg iodine)

Note: Iodized oil may also be given by mouth.

- **Uses**

- Prevention and treatment of iodine deficiency

- **Contraindication**

- Breast-feeding: Appendix C

- **Precautions**

- Those over 45 years old or with nodular goiter (especially susceptible to hyperthyroidism when given iodine supplements; iodized oil may not be appropriate)
 - May interfere with thyroid function tests
 - Pregnancy (see *also* introductory note above): Appendix B

- **Dose**

Endemic moderate-to-severe iodine deficiency, by intramuscular injection

- **ADULT** woman of childbearing age (including any stage of pregnancy): 480 mg once each year

Endemic moderate-to-severe iodine deficiency, by mouth

- **ADULT** woman during pregnancy and one year postpartum: Either 300–480 mg once a year or 100–300 mg every 6 months
- **ADULT** woman of childbearing age: Either 400–960 mg once a year or 200–480 mg every 6 months

Iodine deficiency, by intramuscular injection

- **INFANT** up to 1 year: 190 mg
- **CHILD** and **ADULT**: 380 mg (76 mg in those aged over 45 years or with nodular goiter; *see also under* Precautions) (provides up to 3 years' protection)

Iodine deficiency, by mouth

- **ADULT** (except during pregnancy) and **CHILD** over 6 years: 400 mg once a year
- **ADULT** woman during pregnancy: Single dose of 200 mg
- **INFANT** under 1 year: Single dose of 100 mg
- **CHILD** 1–5 years: 200 mg once a year

- **Adverse effects**
 - Hypersensitivity reactions
 - Goiter and hypothyroidism
 - Hyperthyroidism

- **Multivitamins and minerals**

Multivitamins are a combination of many different vitamins that are normally found in food and other natural sources. Multivitamins are used to provide vitamins that are not taken in through the diet. Multivitamins are also used to treat vitamin deficiencies (lack of vitamins) caused by illness, pregnancy, poor nutrition, digestive disorders, and many other conditions. Majority of the multivitamins contains minerals like calcium, iron, magnesium, potassium, and zinc.

- **Dose**
 - Company guidance, as well as see the relevant drug and table for dosage of any vitamins and minerals for the purpose of prevention and treatment (see reference table below)

Note: Do not use this medicine concomitantly with milk and other dairy products, calcium, or antacids that contain calcium. Calcium may affect the absorption of some components of the multivitamins in the body.

- **Adverse effects**

- Stomach upset, headache, unusual or unpleasant taste in the mouth
- Taking high amounts of minerals changes the color of teeth, increases urination, gastric bleeding, increased heart rate, confusion, muscle weakness or limping.
- The adverse effects of over dosage of vitamins include stomach pain, vomiting, diarrhea, constipation, loss of appetite, hair loss, skin peeling, piercing sensation in and around the mouth, changes in menstruation, body weight loss, severe headache, muscle or joint pain, severe back pain, blood in urine, skin discoloration and bleeding, and damage with minor injuries

- **Multiple micronutrient powder / MNP**

Multiple micronutrient powder contains 15 micronutrients (5 minerals and 10 vitamins).

- **Dosage form**

- Oral ingestion: Multiple micronutrient formulation in the form of 1 g sachet and 500 mg tablets

- **Uses**

- Treatment and prevention of anemia and other micronutrients among children 6–59 months old

- **Contraindications**

- No any specific contraindication
- Only contraindicated in the first phase of the treatment of severe acute malnutrition patients

- **Precaution**

- It can be given to all children, but only three 3 sachets in a week are recommended for children who are taking food fortified with minerals and vitamins.

- **Dose**

- On daily basis, 1 sachet is mixed in pre-prepared food of a child that contains oil and given to him.
- The dose is 60 sachets for 60 days, which provides sufficient micronutrients for a child for 6 months and 120 sachets in a year.

- **Adverse effects**

- No any specific side effects reported
- In some cases, some children develop mild diarrhea and discoloration of stool that are not serious and will disappear with repeated use of the powder.

- **Pyridoxine / vitamin B6**

- **Dosage form**

- Tablets: 25 mg and 40 mg (hydrochloride)
 - Injection: 50 mg/ml in 2 ml ampoule

- **Uses**

- Treatment of pyridoxine deficiency due to metabolic disorders
 - Isoniazid neuropathy
 - Sideroblastic anemia

- **Precautions**

- ***Interactions:*** Appendix A

- **Dose**

Deficiency states, by mouth

- **ADULT:** 25–50 mg up to 3 times daily

Isoniazid neuropathy, prophylaxis, by mouth

- **ADULT:** 10 mg daily

Isoniazid neuropathy, treatment, by mouth

- **ADULT:** 50 mg 3 times daily

Sideroblastic anemia, by mouth

- **ADULT:** 100–400 mg daily in divided doses

- **Adverse effects**

- Generally well tolerated, but chronic administration of high doses may cause peripheral neuropathies

- **Retinol (vitamin A)**

- **Dosage form**

- Capsules and tablets: 50,000 IU, 100,000 IU, and 200,000 IU
- Injection: 50,000 IU and 100,000 IU per ampoule
- Oral oily solution: 100,000 IU

- **Uses**

- Prevention and treatment of vitamin A deficiency
- Prevention of complications of measles

- **Precautions**

- Pregnancy (teratogenic; see *also* introductory note above):

Appendix B

- Breast-feeding: Appendix C

- **Dose**

Prevention of vitamin A deficiency (universal or targeted distribution programs), by mouth

- **ADULT:** 200,000 IU every 6 months
- **ADULT** (pregnant woman): Maximum of 10,000 IU daily or maximum 25,000 IU weekly
- **ADULT** (woman of childbearing age): 200,000 IU at delivery or within 8 weeks of delivery
- **INFANT** under 6 months: 50,000 IU
- **INFANT** 6–12 months: 100,000 IU every 4–6 months, preferably at measles vaccination
- **CHILD** over 1 year (preschool): 200,000 IU every 4–6 months

Note: An additional dose should be given the next day in hospitalized children with measles infection.

Treatment of xerophthalmia, by mouth

- **INFANT** under 6 months: 50,000 IU on diagnosis, repeated the next day and again after 2 weeks
- **INFANT** 6–12 months: 100,000 IU immediately on diagnosis, repeated the next day and again after 2 weeks

- **ADULT** (except woman of childbearing age) and **CHILD** over 1 year: 200,000 IU on diagnosis, repeated the next day and again after 2 weeks
- **ADULT** (woman of childbearing age with severe signs of xerophthalmia): As for other adults; **ADULT** woman of childbearing age with less severe symptoms, for example, night blindness: either 5,000–10,000 IU daily for at least 4 weeks or up to 25,000 IU weekly

Note: Oral vitamin A preparations are preferred for the prevention and treatment of vitamin A deficiency. However, in situations where patients have severe anorexia or vomiting or are suffering from malabsorption, a water-miscible injection preparation may be administered intramuscularly.

- **Adverse effects**

- No serious or irreversible adverse effects at the recommended doses
- High intake may cause birth defects.
- Transient increased intracranial pressure in adults 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.

- **Retinol (vitamin A) + colecalciferol (vitamin D3)**
 - **Dosage form**
 - Topical ointment: Vitamin A 850 IU + vitamin D3 85 IU in 30 g tube
 - **Uses**
 - Diaper rash in neonates and children exposed to urine, superficial burns and burns due to infections, superficial skin irritation and skin dryness
 - **Dose**
 - According to manufacturer's directions
- **Sodium fluoride**
 - **Dosage form**
 - Tablet: 1 mg
 - Oral topical solution: 0.5% in 50 ml bottle
 - Oral topical gel: 0.5% in 60 g tube

Availability of adequate fluoride confers significant resistance to dental caries. It is now considered that the topical action of fluoride on enamel and plaque is more important than its systemic effect. Where the fluoride content of drinking water is less than 700 micrograms/L, daily administration of sodium fluoride

tablets or drops is a suitable means of supplementation. Systemic fluoride supplements should not be prescribed without reference to the fluoride content of the local water supply; infants need not receive fluoride supplements until the age of 6 months at the earliest.

Dentifrices which incorporate sodium fluoride are a convenient source of fluoride. Individuals who are either particularly caries prone or medically compromised may be given additional protection in the form of fluoride rinses or fluoride gels. Rinses may be used daily or weekly; daily use of a less concentrated rinse is more effective than weekly use of a more concentrated one. High-strength gels must be applied on a regular basis under professional supervision; extreme caution is necessary to prevent the child from swallowing any excess.

- **Use**
 - Prevention of dental caries
- **Contraindication**
 - Not for use in areas where drinking water is fluoridated or where fluoride content is naturally high
- **Dose**

Prevention of dental caries, as oral rinse

- **CHILD** over 6 years: 10 ml of a 0.05% solution daily or 10 ml of a 0.2% solution weekly

Note: Fluoridated toothpastes are also a convenient source of fluoride for prophylaxis of dental caries.

- **Adverse effects**

- In recommended doses, toxicity is unlikely.
- Occasionally white flecks on teeth at recommended doses
- Rarely yellowish-brown discoloration if recommended doses are exceeded

Reference table for vitamin and mineral supplements

Acronym	ATC	Name	Form	Therapeutic defined daily dose (adult)	Supplement daily intake		
					Min.	Max.	Unit
Vit A	A11CA01	Retinol	Injection	50 IU	0.4	1.3	mcg
Vit A	A11CA01	Retinol	Oral	50 IU	0.4	1.3	mg
Vit B1 ^a	A11DA01	Thiamine ^a	Injection	50 mg	0.4	1.4	mg
Vit B1 ^a	A11DA01	Thiamine ^a	Oral	50 mg			
Vit B12 ^a	B03BA04	Cobamamide ^a			0.4	2.8	mcg
Vit B12 ^a	B03BA01	Cyanocobalamin ^a	Nas.	0.07 mg	0.4	2.8	mcg
Vit B12 ^a	B03BA01	Cyanocobalamin ^a	Oral	1 mg	0.4	2.8	mcg
Vit B12 ^a	B03BA01	Cyanocobalamin ^a	Injection	0.02 mg	0.4	2.8	mcg
Vit B12 ^a	B03BA02	Cyanocobalamin tannin complex ^a	Injection	0.02 mg	0.4	2.8	mcg
Vit B12 ^a	B03BA03	Hydroxocobalamin ^a	Injection	0.02 mg	0.4	2.8	mcg
Vit B12 ^a	B03BA05	Mecobalamin ^a	Oral	1.5 mg	0.4	2.8	mcg
Vit B12 ^a	B03BA05	Mecobalamin ^a	Injection	0.2 mg	0.4	2.8	mcg
Vit B2 ^a	A11HA04	Riboflavin ^a			0.3	1.6	mg
Vit B3 ^a	A11HA01	Nicotinamide ^a	Oral	150 mg	2	17	mg
Vit B5 ^a	A11HA31	Calcium pantothenate ^a			1.7	7	mg
Vit B5 ^a	A11HA30	Dexpanthenol ^a			1.7	7	mg
Vit B5 ^a	A11HA32	Pantethine ^a			1.7	7	mg
Vit B6 ^a	A11HA06	Pyridoxal phosphate ^a			0.1	2	mg
Vit B6 ^a	A11HA02	Pyridoxine ^a	Oral	160 mg	0.1	2	mg
Vit B6 ^a	A11HA02	Pyridoxine ^a	Injection	160 mg	0.1	2	mg
Vit B7 ^a	A11HA05	Biotin ^a			5	35	mcg
Vit B8 ^a	A11HA07	Inositol ^a					
Vit B9 ^a	B03BB01	Folic acid ^a (prophylaxis)	Oral	0.4 mg	0.065	0.5	mg
Vit B9 ^a	B03BB01	Folic acid ^a (therapy)	Injection	10 mg	0.065	0.5	mg
Vit C ^a	A11GA01	Ascorbic acid ^a	Injection	200 mg	40	120	mg
Vit C ^a	A11GA01	Ascorbic acid ^a	Oral	200 mg	40	120	mg
Vit D	A11CC03	Alfacalcidol	Oral	0.001 mg			
Vit D	A11CC03	Alfacalcidol	Injection	0.001 mg			
Vit D	A11CC06	Calcifediol			5	15	mcg
Vit D	A11CC04	Calcitriol	Oral	0.001 mg			
Vit D	A11CC04	Calcitriol	Injection	0.001 mg			
Vit D	A11CC05	Colecalciferol			5	15	mcg
Vit D	A11CC02	Dihydrotachysterol	Oral	1 mg	5	15	mcg
Vit D	A11CC01	Ergocalciferol			5	15	mcg

Vit D	A11CC07Paricalcitol					
Vit E	A11HA03Tocopherol	Oral	200 mg	4	19	mg
Vit E	A11HA03Tocopherol	Injection	200 mg	4	19	mg
Vit K3	B02BA02Menadione	Oral	10 mg	0.02	0.09	mcg
Vit K3	B02BA02Menadione	Injection	2 mg	0.02	0.09	mcg
Vit K3	B02BA01Phytomenadione	Oral	20 mg	0.02	0.09	mcg
Vit K3	B02BA01Phytomenadione	Injection	20mg	0.02	0.09	mcg
Calcium				210	1,000	mg
Chromium				0.2	45	mcg
Copper				0.34	13	mg
Fluoride				0.01	3	mg
Iodine				0.09	0.29	mg
Iron				0.27	9	mg
Magnesium				0.08	0.32	mg
Manganese				0.003	2.6	mg
Molybdenum				0.017	0.05	mg
Phosphorus				450	700	mg
Selenium				0.02	0.07	mg
Zinc				2	12	mg

^aWater-soluble vitamins may exceed maximum strengths up to 20%.

Source: National Academy of Sciences. 2002. *Dietary Reference Intakes*. Washington, DC: Food and Nutrition Boards, Institute of Medicine, National Academy of Sciences. www.nap.edu

APPENDIX A: Interactions

Two or more drugs given at the same time may interact with each other. The interaction may be potentiation or antagonism of one drug by another, or occasionally some other effect. Drug interactions may be pharmacodynamic or pharmacokinetic.

Pharmacodynamic interactions occur between drugs that have similar or antagonistic pharmacological effects or adverse effects. They are usually predictable from knowledge of the pharmacology of the interacting drugs and given the fact that an interaction occurring with one drug is likely to occur with a related drug. Pharmacodynamic interactions may be due to

- Competition at receptor sites
- Drugs acting on the same physiological system

Pharmacodynamic interactions occur to some extent in most patients who receive the interacting drugs. *Pharmacokinetic interactions* occur when one drug increases or reduces the amount of another drug available to produce its pharmacological action. They are not easily predicted, and an interaction occurring with one drug cannot be assumed to occur with a related drug unless their pharmacokinetic properties are similar. Pharmacokinetic interactions may be due to

- Interference with absorption
- Changes in protein binding
- Modification of drug metabolism
- Interference with renal excretion

Many pharmacokinetic interactions affect only a small proportion of patients taking a combination of interacting drugs.

Many drug interactions do not have serious consequences and many that are potentially harmful occur only in a small proportion of patients. A known interaction will not necessarily occur to the same extent in all patients. Drugs with a small therapeutic-to-toxic ratio (such as phenytoin) and drugs that require careful dose control (such as anticoagulants, antihypertensives, or antidiabetics) are most often involved. Patients at increased risk from drug interactions include the elderly and those with impaired renal or liver function.

In the following table the symbol * indicates a **potentially hazardous interaction** and the combined administration of the drugs involved should be **avoided**, or done only with caution and appropriate monitoring. Interactions with no symbol do not usually have serious consequences.

First medicine	Second medicine	Comment
Abacavir	Methadone	Plasma concentration of methadone possibly reduced
Abacavir	Phenobarbital	Plasma concentration of abacavir possibly reduced
Abacavir	Phenytoin	Plasma concentration of abacavir possibly reduced
Abacavir	Rifampicin	Plasma concentration of abacavir possibly reduced
Aciclovir	Ciclosporin	Increased risk of nephrotoxicity
Acetazolamide	Acetylsalicylic acid	Increased risk of toxicity when given with high-dose acetylsalicylic acid
Acetazolamide	Alcohol	Enhanced hypotensive effect
Acetazolamide	Amitriptyline	Increased risk of postural hypotension
Acetazolamide	Atenolol	Enhanced hypotensive effect
Acetazolamide	Carbamazepine*	Increased risk of hyponatremia; acetazolamide increases plasma carbamazepine concentration
Acetazolamide	Chlorpromazine	Enhanced hypotensive effect

Acetazolamide	Clomipramine	Increased risk of postural hypotension
Acetazolamide	Clonazepam	Enhanced hypotensive effect
Acetazolamide	Contraceptives, Oral	Antagonism of diuretic effect by estrogens
Acetazolamide	Dexamethasone	Increased risk of hypokalemia; antagonism of diuretic effect
Acetazolamide	Diazepam	Enhanced hypotensive effect
Acetazolamide	Digoxin*	Hypokalemia caused by acetazolamide increases cardiac oxicity of digoxin
Acetazolamide	Enalapril*	Enhanced hypotensive effect
Acetazolamide	Ether, anesthetic	Enhanced hypotensive effect
Acetazolamide	Fluphenazine	Enhanced hypotensive effect
Acetazolamide	Furosemide	Increased risk of hypokalemia
Acetazolamide	Glyceryl trinitrate	Enhanced hypotensive effect
Acetazolamide	Halothane	Enhanced hypotensive effect
Acetazolamide	Hydralazine	Enhanced hypotensive effect
Acetazolamide	Hydrocortisone	Increased risk of hypokalemia; antagonism of diuretic effect
Acetazolamide	Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Acetazolamide	Isosorbide dinitrate	Enhanced hypotensive effect
Acetazolamide	Ketamine	Enhanced hypotensive effect
Acetazolamide	Levodopa	Enhanced hypotensive effect
Acetazolamide	Lidocaine*	Hypokalemia caused by acetazolamide antagonizes action of lidocaine (interaction less likely when lidocaine is used topically)
Acetazolamide	Methyldopa	Enhanced hypotensive effect
Acetazolamide	Nifedipine	Enhanced hypotensive effect
Acetazolamide	Nitrous oxide	Enhanced hypotensive effect
Acetazolamide	Phenobarbital	Increased risk of osteomalacia
Acetazolamide	Phenytoin	Increased risk of osteomalacia
Acetazolamide	Prednisolone	Increased risk of hypokalemia;

		antagonism of diuretic effect
Acetazolamide	Propranolol	Enhanced hypotensive effect
Acetazolamide	Quinidine*	Cardiac toxicity of quinidine increased if hypokalemia occurs; acetazolamide possibly reduces excretion of quinidine (increased plasma concentration)
Acetazolamide	Salbutamol	Increased risk of hypokalemia with high doses of salbutamol
Acetazolamide	Sodium nitroprusside	Enhanced hypotensive effect
Acetazolamide	Thiopental	Enhanced hypotensive effect
Acetazolamide	Timolol	Enhanced hypotensive effect
Acetazolamide	Verapamil	Enhanced hypotensive effect
Acetylsalicylic acid	Acetazolamide	Increased risk of toxicity when given with high-dose acetylsalicylic acid
Acetylsalicylic acid	Antacids (Aluminium hydroxide; magnesium hydroxide)	Excretion of acetylsalicylic increased by alkaline urine
Acetylsalicylic acid	Dexamethasone	Increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma salicylate concentration
Acetylsalicylic acid	Enalapril	Antagonism of hypotensive effect; risk of renal impairment when acetylsalicylic acid given in doses of over 300 mg daily
Acetylsalicylic acid	Fluoxetine *	Increased risk of bleeding
Acetylsalicylic acid	Heparin*	Enhanced anticoagulant effect of heparin
Acetylsalicylic acid	Hydrocortisone	Increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma salicylate concentration
Acetylsalicylic acid	Ibuprofen*	Avoid concomitant use (increased adverse effects); antiplatelet effect of acetylsalicylic acid possibly reduced

Acetylsalicylic acid	Methotrexate*	Reduced excretion of methotrexate (increased toxicity)
Acetylsalicylic acid	Metoclopramide	Enhanced effect of acetylsalicylic acid (increased rate of absorption)
Acetylsalicylic acid	Phenytoin	Enhancement of effect of phenytoin
Acetylsalicylic acid	Prednisolone	Increased risk of gastrointestinal bleeding and ulceration; prednisolone reduces plasma salicylate concentration
Acetylsalicylic acid	Spironolactone	Antagonism of diuretic effect
Acetylsalicylic acid	Valproic acid	Enhancement of effect of valproic acid
Acetylsalicylic acid	Warfarin *	Increased risk of bleeding due to antiplatelet effect
Albendazole	Dexamethasone	Plasma albendazole concentration possibly increased
Albendazole	Praziquantel	Increased plasma concentration of active metabolite of albendazole
Alcohol	Acetazolamide	Enhanced hypotensive effect
Alcohol	Amiloride	Enhanced hypotensive effect
Alcohol	Amitriptyline *	Enhanced sedative effect
Alcohol	Atenolol	Enhanced hypotensive effect
Alcohol	Carbamazepine	Possibly enhanced CNS adverse effects of carbamazepine
Alcohol	Chlorphenamine	Enhanced sedative effect
Alcohol	Chlorpromazine	Enhanced sedative effect
Alcohol	Clomipramine *	Enhanced sedative effect
Alcohol	Clonazepam	Enhanced sedative effect
Alcohol	Codeine	Enhanced sedative and hypotensive effect
Alcohol	Cycloserine *	Increased risk of convulsions
Alcohol	Diazepam	Enhanced sedative effect
Alcohol	Enalapril	Enhanced hypotensive effect
Alcohol	Fluoxetine	Possibly enhanced sedative effect
Alcohol	Fluphenazine	Enhanced sedative effect
Alcohol	Furosemide	Enhanced hypotensive effect

Alcohol	Glibenclamide	Enhanced hypoglycaemic effect
Alcohol	Glyceryl trinitrate	Enhanced hypotensive effect
Alcohol	Griseofulvin	Possibly enhanced effects of alcohol
Alcohol	Haloperidol	Enhanced sedative effect
Alcohol	Hydralazine	Enhanced hypotensive effect
Alcohol	Hydrochlorothiazide	Enhanced hypotensive effect
Alcohol	Insulins	Enhanced hypoglycemic effect
Alcohol	Isosorbide dinitrate	Enhanced hypotensive effect
Alcohol	Levamisole	Possibility of disulfiram-like reaction
Alcohol	Metformin	Enhanced hypoglycemic effect; increased risk of lactic acidosis
Alcohol	Methyldopa	Enhanced hypotensive effect
Alcohol	Metronidazole	Disulfiram-like reaction
Alcohol	Morphine	Enhanced sedative and hypotensive effect
Alcohol	Nifedipine	Enhanced hypotensive effect
Alcohol	Paracetamol	Regular or high uptake of alcohol may enhance the risk of hepatic damage
Alcohol	Phenobarbital	Enhanced hypotensive effect
Alcohol	Procarbazine	Disulfiram-like reaction
Alcohol	Promethazine	Enhanced sedative effect
Alcohol	Propranolol	Enhanced hypotensive effect
Alcohol	Sodium nitroprusside	Enhanced hypotensive effect
Alcohol	Spironolactone	Enhanced hypotensive effect
Alcohol	Timolol	Enhanced hypotensive effect
Alcohol	Verapamil	Enhanced hypotensive effect; plasma concentration of alcohol possibly increased by verapamil
Alcohol	Warfarin *	Enhanced anticoagulant effect with large amounts of alcohol; major changes in alcohol consumption may affect anticoagulant control
Allopurinol	Amoxicillin	Increased risk of rash
Allopurinol	Ampicillin	Increased risk of rash
Allopurinol	Azathioprine*	Effects of azathioprine enhanced

		and toxicity increased; educe dose of azathioprine
Allopurinol	Ciclosporin	Plasma ciclosporin concentration possibly increased (risk of nephrotoxicity)
Allopurinol	Hydrochlorothiazide	Increased risk of hypersensitivity, especially in renal impairment
Allopurinol	Mercaptopurine *	Effects of mercaptopurine enhanced and toxicity increased; educe dose of mercaptopurine
Allopurinol	Theophylline	Plasma theophylline concentration possibly increased
Allopurinol	Warfarin	Anticoagulant effect possibly enhanced
Amikacin	Amphotericin B	Enhanced nephrotoxic effects
Amikacin	Capreomycin	Increased risk of nephrotoxicity and ototoxicity
Amikacin	Ciclosporin *	Increased risk of nephrotoxicity
Amikacin	Furosemide *	Increased risk of ototoxicity
Amikacin	Neostigmine *	Antagonism of effects of neostigmine
Amikacin	Pyridostigmine *	Antagonism of effects of pyridostigmine
Amikacin	Suxamethonium *	Enhanced effects of suxamethonium
Amikacin	Vancomycin	Increased risk of nephrotoxicity and ototoxicity
Amikacin	Vecuronium *	Enhanced effects of vecuronium
Aminophylline	Allopurinol	Plasma concentration of aminophylline possibly increased by allopurinol
Aminophylline	Erythromycin	Aminophylline may reduce absorption of oral erythromycin
Aminophylline	Ketoconazole	Plasma concentration of Aminophylline possibly increased by ketoconazole
Aminophylline	Cimetidine	Increase plasma concentration of

		Aminophylline
Amitriptyline	Acetazolamide	Increased risk of postural hypotension
Amitriptyline	Alcohol *	Enhanced sedative effect
Amitriptyline	Amiloride	Increased risk of postural hypotension
Amitriptyline	Atropine	Increased antimuscarinic adverse effects
Amitriptyline	Biperiden	Increased antimuscarinic adverse effects
Amitriptyline	Carbamazepine *	Antagonism of anticonvulsant effect (convulsive threshold lowered); accelerated metabolism of amitriptyline (reduced plasma concentration; reduced antidepressant effect)
Amitriptyline	Chlorphenamine	Increased antimuscarinic and sedative effects
Amitriptyline	Chlorpromazine *	Increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
Amitriptyline	Clonazepam	Enhanced sedative effect
Amitriptyline	Codeine	Possibly enhanced sedative effect
Amitriptyline	Contraceptives, Oral	Antagonism of antidepressant effect by estrogens but adverse effects of amitriptyline possibly increased due to increased plasma concentration of amitriptyline
Amitriptyline	Diazepam	Enhanced sedative effect
Amitriptyline	Epinephrine *	Increased risk of hypertension and arrhythmias (but local anesthetics which contain epinephrine appear to be safe)
Amitriptyline	Ether, anesthetic	Increased risk of hypertension and arrhythmias

Amitriptyline	Ethosuximide *	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Amitriptyline	Fluphenazine *	Increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
Amitriptyline	Furosemide	Increased risk of postural hypotension
Amitriptyline	Glyceryl trinitrate	Reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under tongue owing to dry mouth)
Amitriptyline	Haloperidol *	Increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
Amitriptyline	Halothane	Increased risk of arrhythmias and hypotension
Amitriptyline	Hydralazine	Increased risk of postural hypotension
Amitriptyline	Hydrochlorothiazide	Increased risk of postural hypotension
Amitriptyline	Isosorbide dinitrate	Increased risk of postural hypotension Reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under tongue owing to dry mouth)
Amitriptyline	Ketamine	Increased risk of arrhythmias and hypotension
Amitriptyline	Methyldopa	Increased risk of hypotension
Amitriptyline	Morphine	Possibly increased sedation
Amitriptyline	Nitrous oxide	Increased risk of arrhythmias and hypotension
Amitriptyline	Phenobarbital *	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of amitriptyline possibly accelerated (reduced plasma

		concentration)
Amitriptyline	Phenytoin*	Antagonism of anticonvulsant effect (convulsive threshold lowered); possibly reduced plasma amitriptyline concentration
Amitriptyline	Procainamide *	Increased risk of ventricular arrhythmias
Amitriptyline	Promethazine *	Increased antimuscarinic and sedative effects
Amitriptyline	Quinidine *	Increased risk of ventricular arrhythmias
Amitriptyline	Rifampicin	Plasma concentration of amitriptyline possibly reduced (reduces antidepressant effect)
Amitriptyline	Ritonavir *	Plasma concentration possibly increased by ritonavir
Amitriptyline	Sodium nitroprusside	Increased risk of postural hypotension
Amitriptyline	Spironolactone	Increased risk of postural hypotension
Amitriptyline	Thiopental	Increased risk of arrhythmias and postural hypotension
Amitriptyline	Valproic acid *	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Amitriptyline	Verapamil	Possibly increased plasma concentration of amitriptyline
Amitriptyline	Warfarin *	Enhanced or reduced anticoagulant effect
Amlodipine	Noradrenargic inhibitors	Enhanced hypotensive effect
Amlodipine	Acetazolamide	Enhanced hypotensive effect
Amlodipine	Alcohol	Enhanced hypotensive effect
Amlodipine	Amiloride	Enhanced hypotensive effect
Amlodipine	Atenolol	Enhanced hypotensive effect
Amlodipine	Carbamazepine	Probably reduced effect of amlodipine
Amlodipine	Chlorpromazine	Enhanced hypotensive effect

Amlodipine	Contraceptive,oral	Antagonism of hypotensive effect by estrogens
Amlodipine	Dexamethasone	Antagonism of hypotensive effect
Amlodipine	Diazepam	Enhanced hypotensive effect
Amlodipine	Enalapril	Enhanced hypotensive effect
Amlodipine	Fluphenazine	Enhanced hypotensive effect
Amlodipine	Furosemide	Enhanced hypotensive effect
Amlodipine	Glyceryl trinitrate	Enhanced hypotensive effect
Amlodipine	Haloperidol	Enhanced hypotensive effect
Amlodipine	Halothane	Enhanced hypotensive effect
Amlodipine	Hydralazine	Enhanced hypotensive effect
Amlodipine	Hydrochlorthiazide	Enhanced hypotensive effect
Amlodipine	Hdrocortisone	Antagonism of hypotensive effect
Amlodipine	Ibuprofen	Antagonism of hypotensive effect
Amlodipine	Isosorbide dinitrate	Enhanced hypotensive effect
Amlodipine	Ketamine	Enhanced hypotensive effect
Amlodipine	Levodopa	Enhanced hypotensive effect
Amlodipine	Methyldopa	Enhanced hypotensive effect
Amlodipine	Nitrous oxide	Enhanced hypotensive effect
Amlodipine	Phenobarbital *	Probably reduced effect of amlodipine
Amlodipine	Phenytoin	Probably reduced effect of amlodipine
Amlodipine	Prednisolone	Antagonism of hypotensive effect
Amlodipine	Propranolol	Enhanced hypotensive effect
Amlodipine	Ritonavir *	Possibly increased plasma concentration of amlodipine
Amlodipine	Sodium nitopruside	Enhanced hypotensive effect
Amlodipine	Spironolacton	Enhanced hypotensive effect
Amlodipine	Thiopental	Enhanced hypotensive effect
Amlodipine	Timolol	Enhanced hypotensive effect
Amoxicillin	Allopurinol	Increased risk of rash
Amoxicillin	Contraceptives oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
Amoxicillin	Methotrexate	Reduced excretion of methotrexate

		(increased risk of toxicity)
Amoxicillin	Warfarin	Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of amoxicillin.
Amoxicillin +Clavulanic acid		See Amoxicillin.
Ampicillin	Allopurinol	Increased risk of rash
Ampicillin	Contraceptive,oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
Ampicillin	Methotrexate	Reduced excretion of methotrexate (increased risk of toxicity)
Ampicillin	Warfarin	Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinic is that anticoagulant effect can be possibly enhanced.
Antacids (Aluminium hydroxide; Magnesium hydroxide)		Note: Antacid preferably should not be used concomitantly with other drugs, since they may disturb their absorption.
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Acetyl salicylic acid	Excretion of acetylsalicylic acid increased by alkaline urine
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Azithromycin	Reduced absorption of azithromycin
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Chloroquine	Reduced absorption of chloroquine
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Chlorpromazine	Reduced absorption of chlorpromazine
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Ciprofloxacin	Reduced absorption of ciprofloxacin

Antacids (Aluminium hydroxide; Magnesium hydroxide)	Digoxin	Possibly reduced absorption of digoxin
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Doxycycline	Reduced absorption of doxycycline
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Enalapril	Absorption of enalapril reduced
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Isoniazid	Reduced absorption of isoniazid
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Ofloxacin	Reduced absorption of ofloxacin
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Penicillamine	Reduced absorption of penicillamine
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Phenytoin	Reduced absorption of phenytoin
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Quinidine	Reduced quinidine excretion in alkaline urine (plasma quinidine concentration occasionally increased)
Antacids (Aluminium hydroxide; Magnesium hydroxide)	Rifampicin	Reduced absorption of rifampicin
Atazanavir +Ritonavir	Antacids	Antacids possibly reduce plasma concentration of atazanavir.
Atazanavir +Ritonavir	Amiodarone	Plasma concentration of amiodarone possibly increased
Atazanavir +Ritonavir	Fosamprenavir	Plasma concentration of atazanavir by fosamprenavir
Atazanavir +Ritonavir	Antibacterials	Plasma concentration of both drugs increased when atazanavir given with clarithromycin

Atazanavir +Ritonavir	Rifampicin	Plasma concentration of atazanavir reduced by rifampicin (avoid concomitant use)
Atazanavir +Ritonavir	Warfarin	Atazanavir may enhance or reduce anticoagulant effect of warfarin.
Atazanavir +Ritonavir	Antidepressants	Plasma concentration of atazanavir reduced by St John's wort (avoid concomitant use)
Atazanavir +Ritonavir	Quinine	Atazanavir possibly increases plasma concentration of quinine (increased risk of toxicity).
Atazanavir +Ritonavir	Antimuscarinics	Avoid concomitant use.
Atazanavir +Ritonavir	Aripiprazole	Atazanavir possibly inhibits metabolism of aripiprazole (reduce dose of aripiprazole).
Atazanavir +Ritonavir	Indinavir	Plasma concentration of atazanavir reduced; manufacturer of atazanavir advises avoid concomitant use
Atazanavir +Ritonavir	Nevirapine	Plasma concentration of atazanavir possibly reduced by nevirapine (avoid concomitant use)
Atazanavir +Ritonavir	Maraviroc	Increases plasma concentration of maraviroc (consider reducing dose of maraviroc)
Atazanavir +Ritonavir	Saquinavir	Increased risk of ventricular arrhythmias (manufacturer advise to avoid concomitant use of atazanvir)
Atazanavir +Ritonavir	Midazolam	May increase plasma concentration of midazolam; avoid concomitant oral use
Atazanavir +Ritonavir	Diltiazem	May increase plasma concentration of diltiazem
Atazanavir +Ritonavir	Verapamil	May increase plasma concentration of verapamil
Atazanavir +Ritonavir	Ciclosporin	May increase plasma concentration of ciclosporin
Atazanavir +Ritonavir	Colchicine	Increased risk of colchicine toxicity

		(decrease dose of colchicine); avoid concomitant use in hepatic and renal impairment
Atazanavir +Ritonavir	Atorvastatin	Concomitant use of atazanavir may increase risk of myopathy.
Atazanavir +Ritonavir	Rosuvastatin	Concomitant use of atazanavir with simvastatin may increase risk of myopathy (to avoid concomitant use manufacturers advise rosuvastatin).
Atazanavir +Ritonavir	Simvastatin	Concomitant use of atazanavir with simvastatin may increase risk of myopathy (to avoid concomitant use manufacturers advise simvastatin).
Atazanavir +Ritonavir	Ergot alkaloids	Increased concentration of Ergot Alkaloids by Atazanavir (avoid concomitant use)
Atazanavir +Ritonavir	Ulcer-healing drugs	Plasma concentration of atazanavir decreased by histamine H2-antagonists
Atazanavir +Ritonavir	Tacrolimus	May increase concentration of tacrolimus by atazanavir
Atazanavir +Ritonavir	Ethinylestradiol	May increased plasma concentration of ethinylestradiol
Atazanavir +Ritonavir	Norethistrone	May increase plasma concentration of norethistrone
Atazanavir +Ritonavir	Sildenafil	Side effects of sildenafil may increase by atazanavir
Atazanavir +Ritonavir	Proton pump inhibitors	Proton pump inhibitors may decrease the plasma concentration of atazanavir
Atenolol	Acetazolamide	Enhanced hypotensive effect
Atenolol	Alcohol	Enhanced hypotensive effect
Atenolol	Amiloride	Enhanced hypotensive effect
Atenolol	Amlodipine	Enhanced hypotensive effect
Atenolol	Chlorpromazine	Enhanced hypotensive effect
Atenolol	Clonazepam	Enhanced hypotensive effect
Atenolol	Contraceptives, Oral	Antagonism of hypotensive effect by

		estrogens
Atenolol	Dexamethasone	Antagonism of hypotensive effect
Atenolol	Diazepam	Enhanced hypotensive effect
Atenolol	Digoxin	Increased risk of AV block and bradycardia
Atenolol	Enalapril	Enhanced hypotensive effect
Atenolol	Epinephrine *	Severe hypertension
Atenolol	Ergotamine	Enhanced peripheral vasoconstriction
Atenolol	Ether, Anaesthetic	Enhanced hypotensive effect
Atenolol	Fluphenazine	Enhanced hypotensive effect
Atenolol	Furosemide	Enhanced hypotensive effect
Atenolol	Glibenclamide	Atenolol may mask warning signs of hypoglycemia such as tremor.
Atenolol	Glyceryl trinitrate	Enhanced hypotensive effect
Atenolol	Halothane	Enhanced hypotensive effect
Atenolol	Hydralazine	Enhanced hypotensive effect
Atenolol	Hydrocortisone	Enhanced hypotensive effect
Atenolol	Ibuprofen	Antagonism of hypotensive effect
Atenolol	Insulins	Enhanced hypoglycemic effect; atenolol may mask warning signs of hypoglycaemia such as tremor
Atenolol	Isosorbide dinitrate	Enhanced hypotensive effect
Atenolol	Ketamine	Enhanced hypotensive effect
Atenolol	Levodopa	Enhanced hypotensive effect
Atenolol	Lidocaine *	Increased myocardial depression (interaction less likely when lidocaine used topically)
Atenolol	Metformin	Atenolol may mask warning signs of hypoglycemia such as tremor
Atenolol	Methyldopa	Enhanced hypotensive effect
Atenolol	Nifedipine *	Enhanced hypotensive effect; possibly severe hypotension and heart failure
Atenolol	Nitrous oxide	Enhanced hypotensive effect
Atenolol	Prednisolone	Antagonism of hypotensive effect

Atenolol	Procainamide *	Increased myocardial depression
Atenolol	Quinidine *	Increased myocardial depression
Atenolol	Sodium nitroprusside	Enhanced hypotensive effect
Atenolol	Spironolactone	Enhanced hypotensive effect
Atenolol	Thiopental	Enhanced hypotensive effect
Atenolol	Verapamil *	Asystole, severe hypotension, and heart failure
Atorvastatin	Fosamprenavir	Concomitant use increases risk of myopathy
Atorvastatin	Indinavir	Concomitant use increases risk of myopathy
Atorvastatin	Lopinavir	Concomitant use increases risk of myopathy
Atorvastatin	Ritonavir	Concomitant use increases risk of myopathy
Atorvastatin	Saquinavir	Concomitant use increases risk of myopathy
Atorvastatin	Efavirenz	Decreases plasma concentration of atorvastatin
Atorvastatin	Etravirine	Decreases plasma concentration of atorvastatin
Atorvastatin	Midazolam	May increase plasma concentration of atorvastatin
Atropine	Amitriptyline	Increased antimuscarinic adverse effects
Atropine	Chlorphenamine	Increased antimuscarinic adverse effects
Atropine	Chlorpromazine	Increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration)
Atropine	Clomipramine	Increased antimuscarinic adverse effects
Atropine	Fluphenazine	Increased antimuscarinic adverse effects (but reduced plasma fluphenazine concentration)
Atropine	Glyceryl trinitrate	Possibly reduced effect of

		sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Atropine	Isosorbide dinitrate	Possibly reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Atropine	Levodopa	Absorption of levodopa possibly reduced
Atropine	Metoclopramide	Antagonism of effects of metoclopramide on gastrointestinal activity
Atropine	Neostigmine	Antagonism of effects of neostigmine
Atropine	Promethazine	Increased risk of antimuscarinic adverse effects
Atropine	Pyridostigmine	Antagonism of effects of pyridostigmine
Beclometasone dipropionate	Mifepristone	Possibly reduced effects of inhaled beclometasone for 3–4 days
Benzathine benzylpenicillin	See benzylpenicillin.	
Benzylpenicillin	Contraceptives, oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
Benzylpenicillin	Methotrexate	Reduced excretion of methotrexate (increased risk of toxicity)
Betamethasone		Note: Interactions do not generally apply to corticosteroids used for topical action (including inhalation) unless specified. See Corticosteroids.
Bromocriptine	Alcohol	Tolerance of bromocriptine reduced by alcohol
Bromocriptine	Erythromycin	Plasma concentration of bromocriptine increased by erythromycin (increased risk of toxicity)

Bromocriptine	Macrolides	Plasma concentration of bromocriptine possibly increased by macrolides (increased risk of toxicity)
Bromocriptine	Antipsychotics	Hypoprolactinemic and anti-Parkinsonian effects of bromocriptine antagonized by antipsychotics
Bromocriptine	Domperidone	Hypoprolactinaemic effect of bromocriptine possibly antagonized by domperidone
Bromocriptine	Methyldopa	Anti-Parkinsonian effect of dopaminergics antagonized by methyldopa
Bromocriptine	Metoclopramide	Hypoprolactinaemic effect of bromocriptine antagonized by metoclopramide
Biperiden		Note: Many drugs have antimuscarinic effects; concomitant use of 2 or more such drugs can increase adverse effects such as dry mouth, urine retention, and constipation, and can also lead to confusion especially in the elderly.
Biperiden	Amitriptyline	Increased antimuscarinic adverse effects
Biperiden	Chlorphenamine	Increased antimuscarinic adverse effects
Biperiden	Chlorpromazine	Increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration)
Biperiden	Clomipramine	Increased antimuscarinic adverse effects
Biperiden	Fluphenazine	Increased antimuscarinic adverse effects (but reduced plasma fluphenazine concentration)
Biperiden	Glyceryl trinitrate	Possibly reduced effect of

		sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Biperiden	Isosorbide dinitrate	Possibly reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Biperiden	Levodopa	Absorption of levodopa possibly reduced
Biperiden	Metoclopramide	Antagonism of effects of metoclopramide on gastrointestinal activity
Biperiden	Neostigmine	Antagonism of effects of neostigmine
Biperiden	Pilocarpine	Antagonism of effects of pilocarpine
Biperiden	Promethazine	Increased risk of antimuscarinic adverse effects
Biperiden	Pyridostigmine	Antagonism of effects of pyridostigmine
Bupivacaine	Lidocaine	Increased myocardial depression (interaction less likely when lidocaine used topically)
Bupivacaine	Procainamide	Increased myocardial depression
Bupivacaine	Propranolol*	Increased risk of bupivacaine toxicity
Bupivacaine	Quinidine	Increased myocardial depression
Capreomycin	Amikacin	Increased risk of nephrotoxicity and ototoxicity
Capreomycin	Gentamicin	Increased risk of nephrotoxicity and ototoxicity
Capreomycin	Streptomycin	Increased risk of nephrotoxicity and ototoxicity
Capreomycin	Vancomycin	Increased risk of nephrotoxicity and ototoxicity
Carbamazepine	Acetazolamide*	Increased risk of hyponatraemia; acetazolamide increases plasma carbamazepine concentration

Carbamazepine	Alcohol	Possibly enhanced CNS adverse effects of carbamazepine
Carbamazepine	Amiloride	Increased risk of hyponatraemia
Carbamazepine	Amitriptyline*	Antagonism of anticonvulsant effect (convulsive threshold lowered); accelerated metabolism of amitriptyline (reduced plasma concentration; reduced antidepressant effect)
Carbamazepine	Chloroquine	Possibly increased risk of convulsions
Carbamazepine	Chlorpromazine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Carbamazepine	Ciclosporin*	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
Carbamazepine	Clomipramine*	Antagonism of anticonvulsant effect (convulsive threshold lowered); accelerated metabolism of clomipramine (reduced plasma concentration; reduced antidepressant effect)
Carbamazepine	Clonazepam	May enhance toxic effects, without increasing anticonvulsive effects. Plasma concentration of clonazepam may be decreased.
Carbamazepine	Contraceptives, oral*	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Carbamazepine	Dexamethasone*	Accelerated metabolism of dexamethasone (reduced effect)
Carbamazepine	Doxycycline	Accelerated metabolism of doxycycline (reduced effect)
Carbamazepine	Ergocalciferol	Ergocalciferol requirements possibly increased
Carbamazepine	Erythromycin*	Increased plasma carbamazepine concentration

Carbamazepine	Ethosuximide	May be enhanced toxicity without a corresponding increase in anti-epileptic effect; plasma concentration of ethosuximide possibly reduced
Carbamazepine	Fluoxetine *	Plasma concentration of carbamazepine increased
Carbamazepine	Fluphenazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Carbamazepine	Furosemide	Increased risk of hyponatraemia
Carbamazepine	Haloperidol *	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
Carbamazepine	Hydrochlorothiazide	Increased risk of hyponatremia
Carbamazepine	Hydrocortisone*	Accelerated metabolism of hydrocortisone (reduced effect)
Carbamazepine	Indinavir	Possibly reduced plasma indinavir concentration
Carbamazepine	Isoniazid*	Increased plasma carbamazepine concentration (also isoniazid hepatotoxicity possibly increased)
Carbamazepine	Levonorgestrel*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Carbamazepine	Levothyroxine	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
Carbamazepine	Lopinavir*	Possibly reduced plasma lopinavir concentration
Carbamazepine	Mebendazole	Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection)
Carbamazepine	Medroxyprogesteron*	Accelerated metabolism of

		medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Carbamazepine	Methadone	Reduced plasma concentration of methadone
Carbamazepine	Miconazole	Plasma concentration of carbamazepine possibly increased
Carbamazepine	Nelfinavir	Possibly reduced plasma nelfinavir concentration
Carbamazepine	Nifedipine	Probably reduced effect of nifedipine
Carbamazepine	Norethisterone*	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Carbamazepine	Phenobarbital	May be enhanced toxicity without corresponding increase in antiepileptic effect; reduced plasma concentration of carbamazepine
Carbamazepine	Phenytoin	May be enhanced toxicity without corresponding increase in anti-epileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of carbamazepine often lowered
Carbamazepine	Praziquantel	Plasma praziquantel concentration reduced
Carbamazepine	Prednisolone*	Accelerated metabolism of prednisolone (reduced effect)
Carbamazepine	Ritonavir *	Plasma concentration possibly increased by ritonavir
Carbamazepine	Saquinavir	Possibly reduced plasma saquinavir concentration
Carbamazepine	Spironolactone	Increased risk of hyponatraemia
Carbamazepine	Valproic acid	May be enhanced toxicity without corresponding increase in anti-

		epileptic effect; reduced plasma concentration of valproic acid; plasma concentration of active metabolite of carbamazepine increased
Carbamazepine	Vecuronium	Antagonism of muscle relaxant effect (recovery from neuromuscular blockade accelerated)
Carbamazepine	Verapamil*	Enhanced effect of carbamazepine
Carbamazepine	Warfarin*	Accelerated metabolism of warfarin (reduced anticoagulant effect)
Captopril	Antacid	Antacids reduce absorption of enalapril, captopril.
Chloroquine	Antacids (aluminium hydroxide)	Reduced absorption of chloroquine
Chloroquine	Carbamazepine	Possibly increased risk of convulsions
Chloroquine	Ciclosporin*	Increased plasma ciclosporin concentration (increased risk of toxicity)
Chloroquine	Digoxin*	Plasma digoxin concentration possibly increased
Chloroquine	Ethosuximide	Possibly increased risk of convulsions
Chloroquine	Neostigmine	Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine.
Chloroquine	Phenytoin	Possible increased risk of convulsions
Chloroquine	Praziquante	Plasma praziquantel concentration possibly reduced
Chloroquine	Pyridostigmine	Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of pyridostigmine.
Chloroquine	Quinidine	Increased risk of ventricular

		arrhythmias
Chloroquine	Quinine	Increased risk of ventricular arrhythmias
Chloroquine	Valproic acid*	Possibly increased risk of convulsions
Colchicine	Anti-arrhythmics Amiodarone	Amiodarone possibly increases risk of colchicine toxicity.
Colchicine	Antibacterials	Possible increased risk of colchicine toxicity when given with azithromycin, clarithromycin, erythromycin, and telithromycin (suspend or reduce dose of colchicine; avoid concomitant use in hepatic or renal impairment)
Colchicine	Antifungals	Possible increased risk of colchicine toxicity when given with itraconazole and ketoconazole (suspend or reduce dose of colchicine avoid concomitant use in hepatic or renal impairment)
Colchicine	Antivirals	Possible increased risk of colchicine toxicity when given with atazanavir, indinavir, and ritonavir (suspend or reduce dose of colchicine avoid concomitant use in hepatic or renal impairment)
Colchicine	Calcium-channel blockers	Possible increased risk of colchicine toxicity when given with diltiazem and verapamil (suspend or reduce dose of colchicine avoid concomitant use in hepatic or renal impairment)
Colchicine	Ciclosporin	Possible increased risk of nephrotoxicity and myotoxicity when colchicine given with ciclosporin (suspend or reduce dose of colchicine avoid concomitant use in

		hepatic or renal impairment)
Colchicine	Grapefruit juice	Possible increased risk of colchicine toxicity when given with grapefruit juice
Colchicine	Lipid-regulating drugs	Possible increased risk of myopathy when colchicine given with fibrates or statins
Colestyramine		Other drugs should be taken 1 hour before or 4--6 hours after colestyramine to prevent intervention in their absorption.
Colestyramine	Analgesics	Colestyramine increases the excretion of meloxicam; colestyramine reduces absorption of paracetamol.
Colestyramine	Antibiotics	Colestyramine possibly reduces absorption of tetracycline.
Colestyramine	Vancomycin	Colestyramine antagonizes effects of oral vancomycin.
Colestyramine	Anticoagulant	Colestyramine may enhance or reduce anticoagulant effect of coumarins.
Colestyramine	Antidiabetics	Colestyramine possibly enhances hypoglycemic effect of acarbose.
Colestyramine	Bile acids	Colestyramine possibly reduces absorption of bile acids.
Colestyramine	Cardiac glycosides	Colestyramine possibly reduces absorption of cardiac glycosides.
Colestyramine	Diuretics	Reduces absorption of thiazides
Colestyramine	Anti-epileptics	Colestyramine possibly reduces absorption of valproate.
Colestyramine	Thyroid hormones	Reduces absorption of thyroid hormones
Colestyramine	Meloxicam	Increased excretion of meloxicam
Cycloserine	Alcohol	Increased risk of convulsions
Cycloserine	Isoniazid	Increased risk of CNS toxicity
Calcium salt	Antibiotics	Reduce absorption of tetracycline

		and ciprofloxacin
Calcium salt	Dexamethasone	Reduce absorption of calcium salt
Calcium salt	Digoxin	Large intravenous doses of calcium salts can precipitate arrhythmias.
Calcium salt	Ferrous salts	Reduced absorption of oral ferrous salts
Calcium salt	Hydrochlorothiazide	Increased risk of hypercalemia
Calcium salt	Hydrocortisone	Reduced absorption calcium salts
Calcium salt	Levothyroxine	Reduce absorption of levothyroxine
Calcium salt	Prednisolone	Reduced absorption of calcium salts
Calcium salt	Sodium fluoride	Reduced absorption of sodium flouride
Calcium salt	Zinc sulfate	Reduced absorption of zinc sulfate
Ceftriaxone	Contraceptive, oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
Ceftriaxone	Warfarin *	Possibly enhanced anticoagulant effect
Chloramphenicol	Ciclosporin*	Plasma concentration of ciclosporin possibly increased
Chloramphenicol	Glibenclamide*	Enhanced effect of glibenclamide
Chloramphenicol	Hydroxocobalamin	Response to hydroxocobalamin reduced
Chloramphenicol	Phenobarbital*	Metabolism of chloramphenicol accelerated (reduced plasma chloramphenicol concentration)
Chloramphenicol	Phenytoin *	Plasma phenytoin concentration increased (increased risk of toxicity)
Chloramphenicol	Rifampicin	Accelerated metabolism of chloramphenicol (reduced plasma chloramphenicol concentration)
Chloramphenicol	Warfarin*	Enhanced anticoagulant effect
Chlorphenamine	Alcohol	Enhanced sedative effect
Chlorphenamine	Amitriptyline	Increased antimuscarinic and sedative effects
Chlorphenamine	Atropine	Increased antimuscarinic adverse

		effects
Chlorphenamine	Biperiden	Increased antimuscarinic adverse effects
Chlorphenamine	Clomipramine	Increased antimuscarinic and sedative effects
Chlorphenamine	Clonazepam	Enhanced sedative effect
Chlorphenamine	Diazepam	Enhanced sedative effect
Chlorphenamine	Lopinavir	Possibly increased plasma concentration of chlorphenamine
Chlorpromazine	Acetazolamide	Enhanced hypotensive effect
Chlorphenamine	Alcohol	Enhanced sedative effect
Chlorpromazine	Amiloride	Enhanced hypotensive effect
Chlorpromazine	Amitriptyline*	Increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
Chlorpromazine	Amlodipine	Enhanced hypotensive effect
Chlorpromazine	(Aluminiumhydroxide; magnesiumhydroxide)	Reduced absorption of chlorpromazine
Chlorpromazine	Atenolol	Enhanced hypotensive effect
Chlorpromazine	Atropine	Increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration)
Chlorpromazine	Biperiden	Increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration)
Chlorpromazine	Carbamazepine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Chlorpromazine	Clomipramine*	Increased antimuscarinic adverse effects; increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
Chlorpromazine	Codeine	Enhanced sedative and hypotensive effect

Chlorpromazine	Diazepam	Enhanced sedative effect
Chlorpromazine	Dopamine	Antagonism of hypertensive effect
Chlorpromazine	Enalapril	Enhanced hypotensive effect
Chlorpromazine	Ephedrine	Antagonism of hypertensive effect
Chlorpromazine	Epinephrine	Antagonism of hypertensive effect
Chlorpromazine	Ethosuximide*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Chlorpromazine	Furosemide	Enhanced hypotensive effect
Chlorpromazine	Glibenclamide	Possible antagonism of hypoglycemic effect
Chlorpromazine	Glyceryltrinitrate	Enhanced hypotensive effect
Chlorpromazine	Halothane*	Enhanced hypotensive effect
Chlorpromazine	Hydralazine	Enhanced hypotensive effect
Chlorpromazine	Hydrochlorothiazide	Enhanced hypotensive effect
Chlorpromazine	Isoprenaline	Inhibition of vasoconstrictive effect
Chlorpromazine	Isosorbide dinitrate	Enhanced hypotensive effect
Chlorpromazine	Ketamine*	Enhanced hypotensive effect
Chlorpromazine	Levodopa	Antagonism of effects of levodopa
Chlorpromazine	Methyldopa	Enhanced hypotensive effect; increased risk of extrapyramidal effects
Chlorpromazine	Metoclopramide	Increased risk of extrapyramidal effects
Chlorpromazine	Morphine	Enhanced sedative and hypotensive effect
Chlorpromazine	Nifedipine	Enhanced hypotensive effect
Chlorpromazine	Nitrous oxide*	Enhanced hypotensive effect
Chlorpromazine	Phenobarbital*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Chlorpromazine	Phenytoin*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Chlorpromazine	Procainamide*	Increased risk of ventricular arrhythmias
Chlorpromazine	Propranolol*	Concomitant administration may increase plasma concentration of both drugs; enhanced hypotensive

		effect
Chlorpromazine	Quinidine*	Increased risk of ventricular arrhythmias
Chlorpromazine	Ritonavir*	Plasma concentration possibly increased by ritonavir
Chlorpromazine	Sodium nitroprusside	Enhanced hypotensive effect
Chlorpromazine	Spironolactone	Enhanced hypotensive effect
Chlorpromazine	Thiopental*	Enhanced hypotensive effect
Chlorpromazine	Timolol	Enhanced hypotensive effect
Chlorpromazine	Valproic acid*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Chlorpromazine	Verapamil	Enhanced hypotensive effect
Ciclosporin	Aciclovir	Increased risk of nephrotoxicity
Ciclosporin	Allopurinol	Plasma ciclosporin concentration possibly increased (risk of nephrotoxicity)
Ciclosporin	Amikacin*	Increased risk of nephrotoxicity
Ciclosporin	Amiloride*	Increased risk of hyperkalemia
Ciclosporin	Amphotericin B*	Increased risk of nephrotoxicity
Ciclosporin	Azithromycin*	Plasma concentration of ciclosporin possibly increased
Ciclosporin	Carbamazepine*	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
Ciclosporin	Chloramphenicol*	Plasma concentration of ciclosporin possibly increased
Ciclosporin	Chloroquine*	Increased plasma ciclosporin concentration (increased risk of toxicity)
Ciclosporin	Ciprofloxacin*	Increased risk of nephrotoxicity
Ciclosporin	Colchicine	Increased risk of nephrotoxicity and myotoxicity (plasma concentration of ciclosporin increased)
Ciclosporin	Contraceptives, oral*	Plasma concentration of ciclosporin increased by progestogens and possibly increased by estrogens

Ciclosporin	Digoxin*	Increased plasma concentration of digoxin (increased risk of toxicity)
Ciclosporin	Doxorubicin*	Increased risk of neurotoxicity
Ciclosporin	Doxycycline*	Possibly increased plasma ciclosporin concentration
Ciclosporin	Enalapril*	Increased risk of hyperkalemia
Ciclosporin	Erythromycin*	Increased plasma ciclosporin concentration (inhibition of metabolism of ciclosporin)
Ciclosporin	Fluconazole*	Metabolism of ciclosporin inhibited (increased plasma concentration)
Ciclosporin	Gentamicin*	Increased risk of nephrotoxicity
Ciclosporin	Grapefruit juice*	Increased plasma ciclosporin concentration (risk of toxicity)
Ciclosporin	Griseofulvin	Plasma ciclosporin concentration possibly reduced
Ciclosporin	Hydrochlorothiazide	Increased risk of nephrotoxicity and possibly hypermagnesemia
Ciclosporin	Ibuprofen*	Increased risk of nephrotoxicity
Ciclosporin	Levonorgestrel*	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
Ciclosporin	Medroxyprogesterone*	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
Ciclosporin	Methotrexate*	Increased toxicity
Ciclosporin	Metoclopramide*	Plasma ciclosporin concentration increased
Ciclosporin	Nalidixic acid	Increased risk of nephrotoxicity
Ciclosporin	Nelfinavir*	Possibly increased plasma ciclosporin concentration
Ciclosporin	Nifedipine	Possibly increased plasma nifedipine concentration
Ciclosporin	Norethisterone*	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)

		concentration)
Ciclosporin	Ofloxacin*	Increased risk of nephrotoxicity
Ciclosporin	Phenobarbital*	Metabolism of ciclosporin accelerated (reduced effect)
Ciclosporin	Phenytoin*	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
Ciclosporin	Potassium salts	Increased risk of hyperkalemia
Ciclosporin	Prednisolone*	Increased plasma concentration of prednisolone
Ciclosporin	Rifampicin*	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
Ciclosporin	Ritonavir*	Plasma concentration possibly increased by ritonavir
Ciclosporin	Spironolactone*	Increased risk of hyperkalemia
Ciclosporin	Streptomycin*	Increased risk of nephrotoxicity
Ciclosporin	Sulfadiazine*	Plasma ciclosporin concentration possibly reduced; increased risk of nephrotoxicity
Ciclosporin	Sulfadoxine + pyrimethamine*	Increased risk of nephrotoxicity
Ciclosporin	Sulfamethoxazole + trimethoprim*	Increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim
Ciclosporin	Trimethoprim*	Increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim
Ciclosporin	Vaccine, live*	Avoid use of live vaccines with ciclosporin (impairment of immune response).
Ciclosporin	Vancomycin*	Increased risk of nephrotoxicity
Ciclosporin	Verapamil*	Increased plasma ciclosporin concentration
Ciprofloxacin	Antacids (aluminium	Reduced absorption of ciprofloxacin

	hydroxide; Magnesiumhydroxide)	
Ciprofloxacin	Ciclosporin*	Increased risk of nephrotoxicity
Ciprofloxacin	Contraceptives oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
Ciprofloxacin	Ferrous salts	Absorption of ciprofloxacin reduced by oral ferrous salts
Ciprofloxacin	Glibenclamide	Possibly enhanced effect of glibenclamide
Ciprofloxacin	Ibuprofen*	Possibly increased risk of convulsions
Ciprofloxacin	Morphine	Manufacturer of ciprofloxacin advises to avoid premedication with morphine (reduced plasma ciprofloxacin concentration) when ciprofloxacin used for surgical prophylaxis.
Ciprofloxacin	Phenytoin	Plasma phenytoin concentration can be increased or decreased by ciprofloxacin.
Ciprofloxacin	Warfarin*	Enhanced anticoagulant effect
Ciprofloxacin	Zinc sulfate	Reduced absorption of ciprofloxacin
Clindamycin	Neostigmine	Antagonism of effects of neostigmine
Clindamycin	Pyridostigmine	Antagonism of effects of pyridostigmine
Clindamycin	Suxamethonium*	Enhanced effects of suxamethonium
Clindamycin	Vecuronium*	Enhanced muscle relaxant effect
Clomipramine	Acetazolamide	Increased risk of postural hypotension
Clomipramine	Alcohol*	Enhanced sedative effect
Clomipramine	Amiloride	Increased risk of postural hypotension
Clomipramine	Atropine	Increased antimuscarinic adverse effects

Clomipramine	Biperiden	Increased antimuscarinic adverse effects
Clomipramine	Carbamazepine*	Antagonism of anticonvulsant effect (convulsive threshold lowered); accelerated metabolism of clomipramine (reduced plasma concentration; reduced antidepressant effect)
Clomipramine	Chlorphenamine	Increased antimuscarinic and sedative effects
Clomipramine	Chlorpromazine*	Increased antimuscarinic adverse effects; increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
Clomipramine	Clonazepam	Increased sedative effects
Clomipramine	Codeine	Possibly increased sedation
Clomipramine	Contraceptives, oral	Antagonism of antidepressant effect by estrogens but adverse effects of clomipramine possibly increased due to increased plasma concentration of clomipramine
Clomipramine	Diazepam	Enhanced sedative effect
Clomipramine	Epinephrine*	Increased risk of hypertension and arrhythmias (but local anesthetics which contain epinephrine appear to be safe)
Clomipramine	Ethosuximide*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Clomipramine	Fluphenazine*	Increased antimuscarinic adverse effects; increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
Clomipramine	Furosemide	Increased risk of postural hypotension
Clomipramine	Glyceryl trinitrate	Reduced effect of sublingual

		glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Clomipramine	Haloperidol*	Increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
Clomipramine	Halothane	Increased risk of arrhythmias and hypotension
Clomipramine	Hydralazine	Enhanced hypotensive effect
Clomipramine	Hydrochlorothiazide	Increased risk of postural hypotension
Clomipramine	Isosorbide dinitrate	Reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Clomipramine	Ketamine	Increased risk of arrhythmias and hypotension
Clomipramine	Methyldopa	Enhanced hypotensive effect
Clomipramine	Levothyroxine	Possibly enhanced effects of clomipramine
Clomipramine	Methadone	Sedative effects possibly increased
Clomipramine	Morphine	Possibly increased sedation
Clomipramine	Nitrous oxide	Increased risk of arrhythmias and hypotension
Clomipramine	Phenobarbital*	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of clomipramine possibly accelerated (reduced plasma concentration)
Clomipramine	Phenytoin*	Antagonism of anticonvulsant effect (convulsive threshold lowered); possibly reduced plasma clomipramine concentration
Clomipramine	Procainamide*	Increased risk of ventricular arrhythmias
Clomipramine	Promethazine	Increased antimuscarinic and sedative effects

Clomipramine	Quinidine*	Increased risk of ventricular arrhythmias
Clomipramine	Rifampicin	Plasma concentration of clomipramine possibly reduced
Clomipramine	Ritonavir*	Plasma concentration possibly increased by ritonavir
Clomipramine	Sodium nitroprusside	Enhanced hypotensive effect
Clomipramine	Spironolactone	Increased risk of postural hypotension
Clomipramine	Thiopental	Increased risk of arrhythmias and hypotension
Clomipramine	Valproic acid*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Clomipramine	Verapamil	Possibly increased plasma concentration of clomipramine
Clomipramine	Warfarin	Enhanced or reduced anticoagulant effect
Cloxacillin		See Benzylpenicillin.
Contraceptives, oral		Note: Interactions of combined (estrogen and progestogen) oral contraceptives may also apply to combined parenteral contraceptives.
Contraceptives, oral	Acetazolamide	Antagonism of diuretic effect by estrogens
Contraceptives, oral	Miloride	Antagonism of diuretic effect by estrogens
Contraceptives, oral	Amitriptyline	Antagonism of antidepressant effect by estrogens but adverse effects of amitriptyline possibly increased due to increased plasma concentration of amitriptyline
Contraceptives, oral	Amlodipine	Antagonism of hypotensive effect by estrogens
Contraceptives, oral	Amoxicillin	Contraceptive effect of estrogens possibly reduced (risk probably small)

Contraceptives, oral	Ampicillin	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Atenolol	Antagonism of hypotensive effect by estrogens
Contraceptives, oral	Azithromycin	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Benzylpenicillin	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Carbamazepine*	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Contraceptives, oral	Cefixime	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Ceftazidime	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Ceftriaxone	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Ciclosporin*	Plasma ciclosporin concentration increased by progestogens and possibly increased by estrogens
Contraceptives, oral	Clomipramine	Antagonism of antidepressant effect by estrogens but adverse effects of clomipramine possibly increased due to increased plasma concentration of clomipramine
Contraceptives, oral	Dexamethasone	Oral contraceptives containing estrogens increase plasma concentration of dexamethasone
Contraceptives, oral	Doxycycline	Contraceptive effect of estrogens possibly reduced (risk probably small)

Contraceptives, oral	Efavirenz	Efficacy of estrogen-containing oral contraceptives possibly reduced
Contraceptives, oral	Enalapril	Antagonism of hypotensive effect by estrogens
Contraceptives, oral	Erythromycin	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Furosemide	Antagonism of diuretic effect by estrogens
Contraceptives, oral	Glibenclamide	Antagonism of hypoglycemic effect by estrogens and progestogens
Contraceptives, oral	Glyceryl trinitrate	Antagonism of hypotensive effect by estrogens
Contraceptives, oral	Grisofulvin*	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Contraceptives, oral	Hydralazine	Antagonism of hypotensive effect by estrogens
Contraceptives, oral	Hydrochlorothiazide	Antagonism of diuretic effect by estrogens
Contraceptives, Oral	Hydrocortisone	Oral contraceptives containing estrogens increase plasma concentration of hydrocortisone
Contraceptives, oral	Imipenem + cilastatin	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Insulins	Antagonism of hypoglycemic effect by estrogens and progestogens
Contraceptives, Oral	Isosorbide dinitrate	Antagonism of hypotensive effect by estrogens
Contraceptives, oral	Levofloxacin	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Metformin	Antagonism of hypoglycemic effect by estrogens and progestogens
Contraceptives, oral	Methyldopa	Antagonism of hypotensive effect by estrogens

Contraceptives, oral	Metronidazole	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Nelfinavir*	Accelerated metabolism of estrogens (reduced contraceptive effect); nelfinavir possibly reduces contraceptive effect of progestogens
Contraceptives, oral	Nevirapine*	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Contraceptives, oral	Nifedipine	Antagonism of hypotensive effect by estrogens
Contraceptives, oral	Phenobarbital*	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Contraceptives, oral	Phenoxymethylpenicilin	Contraceptive effect of estrogens possibly reduced (risk probably small)
Contraceptives, oral	Phenytoin*	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Contraceptives, oral	Prednisolone	Oral contraceptives containing estrogens increase plasma concentration of prednisolone
Contraceptives, oral	Propranolol	Antagonism of hypotensive effect by estrogens
Contraceptives, oral	Rifampicine*	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Contraceptives, oral	Ritonavir*	Accelerated metabolism of estrogens (reduced contraceptive effect)
Contraceptives, oral	Sodium nitroprusside	Antagonism of hypotensive effect by estrogens
Contraceptives, oral	Spironolactone	Antagonism of diuretic effect by estrogens
Contraceptives, oral	Theophylline	Delayed excretion of theophylline

		(increased plasma concentration of theophylline)
Contraceptives, oral	Verapamil	Antagonism of hypotensive effect by estrogens
Contraceptives, oral	Warfarin*	Antagonism of anticoagulant effect by estrogens and progestogens
Corticosteroids	ACE inhibitors	Inhibit hypotensive effects of ACE inhibitors by corticosteroid
Corticosteroids	Adrenergic neuron blockers	Inhibit hypotensive effects of adrenergic neuron blockers
Corticosteroids	Aldesleukin	Avoid concomitant manufacturers advised
Corticosteroids	Alpha-blockers	Inhibit hypotensive effects of alpha-blockers
Corticosteroids	Analgesics	Concomitant use of corticosteroids with NSAIDs increase risk of intestinal hemorrhage
Corticosteroids	Aspirin	Concomitant use of corticosteroids with aspirin increases risk of intestinal hemorrhage also corticosteroids reduce the plasma concentration of salicylate.
Corticosteroids	Angiotensin-II receptor Antagonists	Inhibit hypotensive effect of angiotensin-II receptor antagonists
Corticosteroids	Antibiotics clarithromycin	Possibly plasma concentration of methylprednisolone increased by clarithromycin
Corticosteroids	Erythromycin	Possibly corticosteroids metabolic effects inhibit by erythromycin, metabolic of methylprednisolone by erythromycin
Corticosteroids	Isoniazid	Possibly plasma concentration of isoniazid decrease by corticosteroid
Corticosteroids	Rifampicin	Increase metabolic of corticosteroids by rifampicin
Corticosteroids	Anticoagulants	Possibly anticoagulant effect of coumarins decrease by

		corticosteroids; increased effect of inhibitors with high dose of corticosteroids
Corticosteroids	Antidiabetics	Hypoglycemic effect of antidiabetic inhibited by corticosteroids
Corticosteroids	Anti-epileptics	Increase metabolic of corticosteroids by carbamazepine, phenytoin; primedine (decreased effect)
Corticosteroids	Itraconazole	Metabolic of corticosteroids inhibited by itraconazole
Corticosteroids	Ketoconazole	Increase plasma concentration by ketoconazole
Corticosteroids	Momethasone	Increase plasma concentration of momethasone by ketoconazole
Corticosteroids	Methylprednisolone	Inhibited metabolism of prednisolone by ketoconazole
Corticosteroids	Amphotericin	Increased risk of hypokalemia when amphotericin given with corticosteroids (avoid concomitant use)
Corticosteroids	Diuretics	Reduce absorption of thiazides and related diuretics
Dapsone	Rifampicin	Reduced plasma dapsone concentration
Dapsone	Sulfamethoxazole + trimethoprim	Plasma concentration of both dapsone and trimethoprim may increase with concomitant use.
Delavirdine	Phenobarbital	Decrease plasma concentration of delavirdine
Delavirdine	Carbamazepine	Decrease plasma concentration of delavirdine
Delavirdine	Rifampicin	Decrease plasma concentration of delavirdine
Diazepam	Acetazolamide	Enhanced hypotensive effect
Diazepam	Alcohol	Enhanced sedative effect
Diazepam	Amiloride	Enhanced hypotensive effect

Diazepam	Amitriptyline	Enhanced sedative effect
Diazepam	Atenolol	Enhanced hypotensive effect
Diazepam	Chlorphenamine	Enhanced sedative effect
Diazepam	Chlorpromazine	Enhanced sedative effect
Diazepam	Clomipramine	Enhanced sedative effect
Diazepam	Codeine	Enhanced sedative effect
Diazepam	Enalapril	Enhanced hypotensive effect
Diazepam	Ether, anesthetic	Enhanced sedative effect
Diazepam	Fluphenazine	Enhanced sedative effect
Diazepam	Furosemide	Enhanced hypotensive effect
Diazepam	Glyceryl trinitrate	Enhanced hypotensive effect
Diazepam	Haloperidol	Enhanced sedative effect
Diazepam	Halothane	Enhanced sedative effect
Diazepam	Hydralazine	Enhanced hypotensive effect
Diazepam	Hydrochlorothiazide	Enhanced hypotensive effect
Diazepam	Isoniazid	Metabolism of diazepam inhibited
Diazepam	Isosorbide dinitrate	Enhanced hypotensive effect
Diazepam	Ketamine	Enhanced sedative effect
Diazepam	Levodopa	Possibly antagonism of levodopa effects
Diazepam	Methyldopa	Enhanced hypotensive effect
Diazepam	Morphine	Enhanced sedative effect
Diazepam	Nifedipine	Enhanced hypotensive effect
Diazepam	Nitrous oxide	Enhanced sedative effect
Diazepam	Phenytoin	Plasma phenytoin concentration possibly increased or decreased by diazepam
Diazepam	Promethazine	Enhanced sedative effect
Diazepam	Propranolol	Enhanced hypotensive effect
Diazepam	Rifampicin	Metabolism of diazepam accelerated (reduced plasma concentration)
Diazepam	Ritonavir*	Plasma concentration possibly increased by ritonavir (risk of extreme sedation and respiratory depression—avoid concomitant use)

Diazepam	Sodium nitroprusside	Enhanced hypotensive effect
Diazepam	Spironolactone	Enhanced hypotensive effect
Diazepam	Thiopental	Enhanced sedative effect
Diazepam	Timolol	Enhanced hypotensive effect
Diazepam	Verapamil	Enhanced hypotensive effect
Diclofenac	ACE inhibitors	Increased risk of hyperkalemia when ciclosporin given with angiotensin-II receptor antagonists, risk of hypotension
Diclofenac	ACE inhibitors	Risk of reduce hypotensive effect
Diclofenac	Adrenergic Neuron Blockers	Increased risk of hyperkalemia when ciclosporin given with angiotensin-II receptor antagonists, risk of reduce hypotensive effect
Diclofenac	Angiotensin-II receptor antagonists	Risk of antagonism to hypotensive effect
Diclofenac	Alpha-blockers	Reduce their hypotensive effects
Diclofenac	Aspirin	Avoid concomitant use of NSAIDs with aspirin and other NSAIDs due to increase side effects
Diclofenac	Angiotensin receptor antagonists	Possibly increased risk renal impairment and decreased hypotensive effects
Diclofenac	Quinolone	Increased risk of convulsion
Diclofenac	Coumarins anticoagulant	Possibly increased anticoagulant effect of coumarins; also diclofenac injection increased risk of hemorrhage (concomitant use should be avoided)
Diclofenac	Heparin anticoagulant	Avoid concomitant use with heparin (even in small amount), possibly concomitant use with NSAIDs increase risk of hemorrhage
Diclofenac	Antidepressants (selective serotonin reuptake inhibitors) SSRIs	Concomitant use with antidepressant medicines possibly increases risk of hemorrhage

Diclofenac	Beta-blockers	Antagonizes hypotensive effect
Diclofenac	Calcium-channel blockers	Antagonizes hypotensive effect of calcium-channel blockers
Diclofenac	Cardiac glycoside digoxin	Possibly increased plasma concentration of cardiac glycoside, also increased risk of CHF and decreased renal function
Diclofenac	Cyclosporin	Increased risk of nephrotoxicity; plasma concentration of diclofenac increased by cyclosporine (half the dose of diclofenac)
Diclofenac	Clonidine	Antagonizes hypotensive effect of clonidine
Diclofenac	Clopidogrel	Increased risk of hemorrhage
Diclofenac	Corticosteroids	Increased risk of hemorrhage and peptic ulcers
Diclofenac	Methotrexate	Concomitant use of cytotoxic decrease excretion of methotrexate (increase toxicity)
Diclofenac	Diazoxide	Antagonizes hypotensive effect of diazoxide
Diclofenac	Diuretics	Risk of nephrotoxicity of NSAIDs in concomitant use increased by diuretics; also antagonism of diuretic effect; also concomitant use of NSAIDs with potassium-sparing diuretics increases risk of hyperkalemia
Diclofenac	Sulfonureas	Possibly increased effect of sulfonureas
Diclofenac	Potassium-sparing diuretics	Possibly increased risk of hyperkalemia
Diclofenac	Methyldopa	Antagonizes hypotensive effect of methyldopa
Diclofenac	Nitrates	Antagonizes hypotensive effect of nitrates
Diclofenac	Penicillamine	Increased nephrotoxicity

Diclofenac	Vasodilators, hypertensives	Antagonizes hypotensive effect of hydralazine, minoxidil and sodium nitroprusside
Digoxin	Acetazolamide*	Hypokalemia caused by acetazolamide increases cardiac toxicity of digoxin.
Digoxin	Amphotericin B*	Hypokalemia caused by amphotericin B increases cardiac toxicity of digoxin.
Digoxin	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Possibly reduced absorption of digoxin
Digoxin	Atenolol	Increased risk of AV block and bradycardia
Digoxin	Azithromycin	Increased plasma concentration of digoxin (increased risk of toxicity)
Digoxin	Calcium salts	Large intravenous doses of calcium salts can precipitate arrhythmias
Digoxin	Chloroquine*	Plasma digoxin concentration possibly increased
Digoxin	Ciclosporin*	Increased plasma concentration of digoxin (increased risk of toxicity)
Digoxin	Dexamethasone	Increased risk of hypokalemia
Digoxin	Erythromycin	Increased plasma concentration of digoxin (increased risk of toxicity)
Digoxin	Furosemide*	Hypokalemia caused by furosemide increases cardiac toxicity of digoxin
Digoxin	Gentamicin	Possibly increased plasma concentration of digoxin
Digoxin	Hydrochlorothiazide*	Hypokalemia caused by hydrochlorothiazide increases cardiac toxicity of digoxin
Digoxin	Hydrocortisone	Increased risk of hypokalemia
Digoxin	Ibuprofen	Possibly exacerbation of heart failure, reduced renal function, and increased plasma digoxin concentration

Digoxin	Nifedipine*	Possibly increased plasma concentration of digoxin
Digoxin	Penicillamine	Plasma concentration of digoxin possibly reduced
Digoxin	Phenytoin	Plasma concentration of digoxin possibly reduced
Digoxin	Prednisolone	Increased risk of hypokalemia
Digoxin	Propranolol	Increased risk of AV block and bradycardia
Digoxin	Quinidine*	Plasma concentration of digoxin increased (halve the dose of digoxin)
Digoxin	Quinine*	Plasma concentration of digoxin increased
Digoxin	Rifampicin	Plasma concentration of digoxin possibly reduced
Digoxin	Salbutamol	Possibly reduced plasma concentration of digoxin
Digoxin	Spironolactone*	Plasma concentration of digoxin increased
Digoxin	Sulfamethoxazole + trimethoprim	Plasma concentration of digoxin possibly increased
Digoxin	Sulfasalazine	Absorption of digoxin possibly reduced
Digoxin	Suxamethonium	Risk of ventricular arrhythmias
Digoxin	Timolol	Increased AV block and bradycardia
Digoxin	Trimethoprim	Plasma concentration of digoxin possibly increased
Digoxin	Verapamil*	Increased plasma concentration of digoxin; increased AV block and bradycardia
Diphenhydramine hydrochloride	Metoprolol	Decreased metabolism of liver
Diphenhydramine hydrochloride	Venlafaxine	Decreased liver metabolism of venlafaxine
Diphenhydramine teoclate	Alcohol, barbiturates,	Possibly increases the sedative

	hypnotics, opioide analgesics, sedatives and antipsychotics	effect of alcohol, barbiturates, hypnotics, opioids analgesics, sedatives, and antipsychotic medicines
Dopamine	Chlorpromazine	Antagonism of hypertensive effect
Dopamine	Ergometrine	Increased risk of ergotism
Dopamine	Fluphenazine	Antagonism of hypertensive effect
Dopamine	Haloperidol	Antagonism of hypertensive effect
Doxycycline	Antacids (aluminium hydroxide; magnesium hydroxide)	Reduced absorption of doxycycline
Doxycycline	Carbamazepine	Accelerated metabolism of doxycycline (reduced effect)
Doxycycline	Ciclosporin*	Possibly increased plasma ciclosporin concentration
Doxycycline	Contraceptives, oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
Doxycycline	Ferrous salts	Absorption of oral ferrous salts reduced by doxycycline; absorption of doxycycline reduced by oral ferrous salts
Doxycycline	Methotrexate	Increased risk of methotrexate toxicity
Doxycycline	Phenobarbital	Metabolism of doxycycline accelerated (reduced plasma concentration)
Doxycycline	Phenytoin	Increased metabolism of doxycycline (reduced plasma concentration)
Doxycycline	Rifampicin	Plasma doxycycline concentration possibly reduced
Doxycycline	Warfarin*	Anticoagulant effect possibly enhanced
Enalapril	Acetazolamide*	Enhanced hypotensive effect
Enalapril	Acetylsalicylicacid	Antagonism of hypotensive effect; risk of renal impairment when

		acetylsalicylic acid given in doses of over 300 mg daily
Enalapril	Alcohol	Enhanced hypotensive effect
Enalapril	Amiloride*	Enhanced hypotensive effect; increased risk of severe hyperkalaemia
Enalapril	Amlodipine	Enhanced hypotensive effect
Enalapril	Antacids (Aluminium hydroxide; magnesium hydroxide)	Absorption of enalapril reduced
Enalapril	Atenolol	Enhanced hypotensive effect
Enalapril	Chlorpromazine	Enhanced hypotensive effect
Enalapril	Ciclosporin*	Increased risk of hyperkalemia
Enalapril	Clonazepam	Enhanced hypotensive effect
Enalapril	Contraceptives, oral	Antagonism of hypotensive effect by estrogens
Enalapril	Dexamethasone	Antagonism of hypotensive effect
Enalapril	Diazepam	Enhanced hypotensive effect
Enalapril	Ether, anesthetic	Enhanced hypotensive effect
Enalapril	Ethinylestradiol	Antagonise hypotensive effect
Enalapril	Fluphenazine	Enhanced hypotensive effect
Enalapril	Furosemide*	Enhanced hypotensive effect
Enalapril	Glibenclamide	Hypoglycaemic effect possibly enhanced
Enalapril	Glyceryl trinitrate	Enhanced hypotensive effect
Enalapril	Haloperidol	Enhanced hypotensive effect
Enalapril	Halothane	Enhanced hypotensive effect
Enalapril	Heparin	Increased risk of hyperkalemia
Enalapril	Hydralazine	Enhanced hypotensive effect
Enalapril	Hydrochlorothiazide*	Enhanced hypotensive effect
Enalapril	Hydrocortisone	Antagonism of hypotensive effect
Enalapril	Ibuprofen	Antagonism of hypotensive effect; increased risk of renal impairment
Enalapril	Insulins	Hypoglycemic effect possibly enhanced
Enalapril	Isosorbide dinitrate	Enhanced hypotensive effect

Enalapril	Ketamine	Enhanced hypotensive effect
Enalapril	Levodopa	Enhanced hypotensive effect
Enalapril	Metformin	Hypoglycaemic effect possibly enhanced
Enalapril	Methyldopa	Enhanced hypotensive effect
Enalapril	Nifedipine	Enhanced hypotensive effect
Enalapril	Nitrous oxide	Enhanced hypotensive effect
Enalapril	Potassium salts*	Increased risk of severe hyperkalemia
Enalapril	Prednisolone	Antagonism of hypotensive effect
Enalapril	Propranolol	Enhanced hypotensive effect
Enalapril	Sodium nitroprusside	Enhanced hypotensive effect
Enalapril	Spironolactone*	Enhanced hypotensive effect; increased risk of severe hyperkalemia (monitor plasma potassium concentration with low-dose spironolactone in heart failure)
Enalapril	Thiopental	Enhanced hypotensive effect
Enalapril	Timolol	Enhanced hypotensive effect
Enalapril	Verapamil	Enhanced hypotensive effect
Enoxaparin	See Heparin.	
Epinephrine (adrenaline)	Amitriptyline*	Increased risk of hypertension and arrhythmias (but local anesthetics that contain epinephrine appear to be safe)
Epinephrine (adrenaline)	Atenolol*	Severe hypertension
Epinephrine (adrenaline)	Chlorpromazine	Antagonism of hypertensive effect
Epinephrine (adrenaline)	Dexamethasone	Accelerate metabolism of dexamethason
Epinephrine (adrenaline)	Clomipramine*	Increased risk of hypertension and arrhythmias (but local anesthetics which contain epinephrine appear to be safe)
Epinephrine (adrenaline)	Ergotamine	Increased risk of ergotism
Epinephrine (adrenaline)	Ether, Anesthetic	Risk of arrhythmia
Epinephrine (adrenaline)	Fluphenazine	Antagonism of hypertensive effect

Epinephrine (adrenaline)	Haloperidol	Antagonism of hypertensive effect
Epinephrine (adrenaline)	Halothane*	Risk of arrhythmias
Epinephrine (adrenaline)	Oxytocin	Risk of hypertension due to enhanced vasopressor effect of epinephrine
Epinephrine (adrenaline)	Propranolol*	Severe hypertension
Epinephrine (adrenaline)	Timolol*	Severe hypertension
Ergometrine	Dopamine	Increased risk of ergotism
Ergometrine	Halothane	Reduced effect of ergometrine on parturient uterus
Ergometrine	Efavirenz*	Increased risk of ergotism (avoid concomitant use)
Ergotamine	Atenolol	Increased peripheral vasoconstriction
Ergotamine	Azithromycin	Increased risk of ergotism (avoid concomitant use)
Ergotamine	Doxycycline	Increased risk of ergotism
Ergotamine	Ephedrine	Increased risk of ergotism
Ergotamine	Epinephrine	Increased risk of ergotism
Ergotamine	Erythromycin	Increased risk of ergotism (avoid concomitant use)
Ergotamine	Indinavir	Increased risk of ergotism (avoid concomitant use)
Ergotamine	Isoprenaline	Increased risk of ergotism
Ergotamine	Nelfinavir	Increased risk of ergotism (avoid concomitant use)
Ergotamine	Propranolol	Increased peripheral vasoconstriction
Ergotamine	Ritonavir	Increased risk of ergotism (avoid concomitant use)
Ergotamine	Saquinavir	Possibly increased risk of ergotism (avoid concomitant use)
Ergotamine	Timolol	Increased peripheral vasoconstriction
Erythromycin	Carbamazepine*	Increased plasma carbamazepine concentration

Erythromycin	Ciclosporin*	Increased plasma ciclosporin concentration (inhibition of metabolism of ciclosporin)
Erythromycin	Contraceptives, oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
Erythromycin	Dexamethasone	Erythromycin possibly inhibits metabolism of dexamethasone.
Erythromycin	Digoxin	Increased plasma concentration of digoxin (increased risk of toxicity)
Erythromycin	Ergotamine	Increased risk of ergotism (avoid concomitant use)
Erythromycin	Hydrocortisone	Erythromycin possibly inhibits metabolism of hydrocortisone.
Erythromycin	Prednisolone	Erythromycin possibly inhibits metabolism of prednisolone.
Erythromycin	Quinidine*	Increased risk of ventricular arrhythmias with parenteral erythromycin
Erythromycin	Ritonavir	Plasma concentration possibly increased by ritonavir
Erythromycin	Simvastatin*	Increased risk of myopathy
Erythromycin	Theophylline	Inhibits metabolism of theophylline (increased plasma concentration), if erythromycin given by mouth, also decreased plasma-erythromycin concentration
Erythromycin	Valproic acid	Metabolism of valproic acid possibly inhibited (increased plasma concentration)
Erythromycin	Verapamil*	Possible inhibition of metabolism of verapamil (increased risk of toxicity)
Erythromycin	Vinblastine*	Increased toxicity of vinblastine (avoid concomitant use)
Erythromycin	Warfarin*	Enhanced anticoagulant effect
Ethinylestradiol	See Contraceptives,	

	oral.	
Ethosuximide	Amitriptyline*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Ethosuximide	Carbamazepine	May be enhanced toxicity without corresponding increase in antiepileptic effect; possibly reduced plasma concentration of ethosuximide
Ethosuximide	Chloroquine*	Possibly increased risk of convulsions
Ethosuximide	Chlorpromazine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Ethosuximide	Clomipramine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Ethosuximide	Fluphenazine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Ethosuximide	Haloperidol*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Ethosuximide	Isoniazid*	Metabolism of ethosuximide inhibited (increased plasma ethosuximide concentration and risk of toxicity)
Ethosuximide	Phenobarbital*	May be enhanced toxicity without corresponding increase in anti-epileptic effect; possibly reduced plasma concentration of ethosuximide
Ethosuximide	Phenytoin*	May be enhanced toxicity without corresponding increase in anti-epileptic effect; plasma concentration of phenytoin possibly increased; plasma concentration of ethosuximide possibly reduced
Ethosuximide	Valproic acid	There may be enhanced toxicity without corresponding increase in anti-epileptic effect; possibly increased plasma concentration of

		ethosuximide.
Ferrous salts	Ciprofloxacin	Absorption of ciprofloxacin reduced by oral ferrous salts
Ferrous salts	Doxycycline	Absorption of oral ferrous salts reduced by doxycycline; absorption of doxycycline reduced by oral ferrous salts
Ferrous salts	Dimercaprol *	Avoid concomitant use.
Ferrous salts	Levodopa	Absorption of oral ferrous salts reduced by doxycycline; absorption of doxycycline reduced by oral ferrous salts; absorption of levodopa may be reduced by oral ferrous salts
Ferrous salts	Methyldopa	Oral ferrous salts reduce hypotensive effect of methyldopa
Ferrous salts	Ofloxacin	Absorption of ofloxacin reduced by oral ferrous salts
Ferrous salts	Penicillamine	Oral ferrous salts reduce absorption of penicillamine
Ferrous salts	Zinc sulfate	Absorption of zinc and of oral ferrous salts reduced
Fibrates	Daptomycin	Increased risk of myopathy when fibrates given with daptomycin (preferably avoid concomitant use)
Fibrates	Antibiotics	Increased risk of myopathy (preferably avoid concomitant use)
Fibrates	Anticoagulants, coumarins,	Fibrates enhance anticoagulant effect of coumarins.
Fibrates	Antidiabetics, insulin, or sulfonylureas	Fibrates may improve glucose tolerance and have an additive effect with insulin or sulfonylureas.
Fibrates	Ciclosporin	Increased risk of renal impairment when bezafibrate or fenofibrate given with ciclosporin
Fibrates	Colchicine	Possible increased risk of myopathy when fibrates given with colchicine

		(avoid concomitant use)
Fibrates	Cytotoxics	Gemfibrozil increases plasma concentration of bexarotene; avoid concomitant use.
Fibrates	Antagonist receptors of leukotriene	Gemfibrozil increases montelukast plasma concentration.
Fenofibrate (fibrates)	Lipid-regulating drugs	Increased risk of myopathy when dapsomycin given with statins (preferably avoid concomitant use)
Fibrates	Atrovastatin, fluvastatin, veravastatin	Increased risk of myopathy when gemfibrozil given with atrovastatin, fluvastatin, and veravastatin
Fibrates	Rosavastatin	Increased risk of myopathy when concomitant use with rosvastatin
Fibrates	Simvastatine	Increased risk of myopathy when bisafibrate and ciprofibrate given with simvastatine (avoid concomitant use)
Fibrates	Statins	Increased risk of myopathy in concomitant use of fibrates with statins
Fluorouracil	Metronidazole	Metabolism of fluorouracil inhibited (increased toxicity)
Fluorouracil	Phenytoin	Metabolism of phenytoin possibly inhibited (increased risk of toxicity)
Fluorouracil	Vaccine, live	Avoid use of live vaccines with fluorouracil (impairment of immune response).
Fluorouracil	Warfarin *	Anticoagulant effect possibly enhanced
Fluoxetine	Alcohol	Possibly increased sedation
Fluoxetine	Haloperidol*	Plasma concentration of haloperidol increased
Fluoxetine	Aspirin and other NSAIDs	If used concomitantly, may increase risk of bleeding.
Fluoxetine	Tramadol	Concomitant use increases neurotoxicity.

Fluoxetine	Ibuprofen*	Increased risk of bleeding
Fluoxetine	Coumarin	May increase anticoagulant effects of coumarin
Fluoxetine	Monamine oxidase inhibitors (MAOIs)	Fluoxetine should not be given until 2 weeks of MAOs therapy, or MAOs should not be started until 5 months of fluoxetin therapy.
Fluoxetine	Anti-epileptics	May inhibit anti-epileptic effects fo drugs
Fluoxetine	Carbamazepine*	Increase plasma concentration of carbamazepine
Fluoxetine	Phenytoin*	Plasma concentration of phenytoin increased
Fluoxetine	Cyproheptadine	Its antidepressant effect is inhibited by cyproheptadine.
Fluoxetine	Antipsychotics	Fluoxetine may increase plasma concentration of clozapine, haloperidol, and risperidon.
Fluoxetine	Phenobarbital	Antagonism of anticonvulsive effect (convulsive threshold lowered)
Fluoxetine	Ritonavir*	Plasma concentration of fluoxetine possibly increased
Fluoxetine	Warfarin*	Anticoagulant effect possibly enhanced
Fluphenazine	Acetazolamide	Enhanced hypotensive effect
Fluphenazine	Alcohol	Enhanced sedative effect
Fluphenazine	Amiloride	Enhanced hypotensive effect
Fluphenazine	Amitriptyline*	Increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
Fluphenazine	Amlodipine	Enhanced hypotensive effect
Fluphenazine	Antacid	Reduced absorption of fluphenazine
Fluphenazine	Atenolol	Enhanced hypotensive effect

Fluphenazine	Atropine	Increased antimuscarinic adverse effects (but reduced plasma fluphenazine concentration)
Fluphenazine	Biperiden	Increased antimuscarinic adverse effects (but reduced plasma fluphenazine concentration)
Fluphenazine	Carbamazepine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Fluphenazine	Clomipramine*	Increased antimuscarinic adverse effects; increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
Fluphenazine	Clonazepam	Increased sedative effects
Fluphenazine	Codeine	Enhanced sedative and hypotensive effect
Fluphenazine	Diazepam	Enhanced sedative effect
Fluphenazine	Dopamine	Antagonism of hypertensive effect
Fluphenazine	Enalapril	Enhanced hypotensive effect
Fluphenazine	Ephedrine	Antagonism of hypertensive effect
Fluphenazine	Epinephrine	Antagonism of hypertensive effect
Fluphenazine	Ether, anesthetic	Increased hypotensive effects
Fluphenazine	Ethosuximide*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Fluphenazine	Furosemide	Enhanced hypotensive effect
Fluphenazine	Glibenclamide	Possible antagonism of hypoglycemic effect
Fluphenazine	Glyceryl trinitrate	Enhanced hypotensive effect
Fluphenazine	Halothane*	Enhanced hypotensive effect
Fluphenazine	Hydralazine	Enhanced hypotensive effect
Fluphenazine	Hydrochlorothiazide	Enhanced hypotensive effect
Fluphenazine	Isoprenaline	Enhanced hypotensive effect
Fluphenazine	Isosorbide dinitrate	Enhanced hypotensive effect
Fluphenazine	Ketamine*	Enhanced hypotensive effect
Fluphenazine	Levodopa	Antagonism of effects of levodopa
Fluphenazine	Methadone	Enhanced hypotensive and sedative

		effects
Fluphenazine	Methyldopa	Enhanced hypotensive effect; increased risk of extrapyramidal effects
Fluphenazine	Metoclopramide	Increased risk of extrapyramidal effects
Fluphenazine	Morphine	Enhanced sedative and hypotensive effect
Fluphenazine	Nifedipine	Enhanced hypotensive effect
Fluphenazine	Nitrous oxide*	Enhanced hypotensive effect
Fluphenazine	Phenobarbital*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Fluphenazine	Phenytoin*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Fluphenazine	Procainamide*	Increased risk of ventricular arrhythmias
Fluphenazine	Propranolol	Enhanced hypotensive effect
Fluphenazine	Quinidine*	Increased risk of ventricular arrhythmias
Fluphenazine	Ritonavir*	Plasma concentration possibly increased by ritonavir
Fluphenazine	Sodium nitroprusside	Enhanced hypotensive effect
Fluphenazine	Spironolactone	Enhanced hypotensive effect
Fluphenazine	Thiopental*	Enhanced hypotensive effect
Fluphenazine	Timolol	Enhanced hypotensive effect
Fluphenazine	Valproic acid*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Fluphenazine	Verapamil	Enhanced hypotensive effect
Folic acid	Phenobarbital	Plasma concentration of phenobarbital possibly reduced
Folic acid	Phenytoin	Plasma phenytoin concentration possibly reduced
Folic acid	Sulfasalazine	Possibly reduced absorption of folic acid
Fosamprenavir + ritonavir: fosamprenavir is a prodrug of amprenavir		
Fosamprenavir + ritonavir	Methadone	Fosamprenavir reduces plasma

		concentration of methadone.
Fosamprenavir + ritonavir	Amiodarone	Fosamprenavir possibly increases plasma concentration of amiodarone.
Fosamprenavir + ritonavir	Lidocaine	Fosamprenavir possibly increases plasma concentration of lidocaine (avoid concomitant use).
Fosamprenavir + ritonavir	Anticoagulants, coumarin	Fosamprenavir may enhance or reduce anticoagulant effect of coumarins.
Fosamprenavir + ritonavir	Antidepressants	Plasma concentration of fosamprenavir reduced (avoid concomitant use)
Fosamprenavir + ritonavir	Anti-epileptics, carbamazepine	Plasma concentration of fosamprenavir possibly reduced by carbamazepine
Fosamprenavir + ritonavir	Antifungals, ketoconazole	Fosamprenavir increases plasma concentration of ketoconazole (also plasma concentration of fosamprenavir possibly increased); plasma concentration of both drugs may increase when fosamprenavir given with itraconazole.
Fosamprenavir + ritonavir	Antimalarials	Possibly increases plasma concentration of quinine (increased risk of toxicity).
Fosamprenavir + ritonavir	Antimuscarinics	avoidance of fosamprenavir advised by manufacturer of darifenacin and tolterodine
Fosamprenavir 700 mg + ritonavir	Antipsychotics aripiprazole	Inhibits metabolism of aripiprazole (reduce dose of aripiprazole)
Fosamprenavir + ritonavir	Antivirals, efavirenz	Plasma concentration of fosamprenavir reduced by efavirenz
Fosamprenavir + ritonavir	Etravirine	Plasma concentration of fosamprenavir increased by etravirine
Fosamprenavir + ritonavir	Lopinavir	Plasma concentration of

		fosamprenavir reduced by lopinavir (avoid concomitant use)
Fosamprenavir 700 mg + ritonavir	Nevirapine	Plasma concentration of fosamprenavir possibly reduced by nevirapine
Fosamprenavir 700 mg + ritonavir	Anxiolytics and hypnotics	Possibly increases plasma concentration of midazolam risk of prolonged sedation (avoid concomitant use).
Fosamprenavir + ritonavir	Barbiturates Phenobarbital	Plasma concentration of fosamprenavir possibly reduced by phenobarbital
Fosamprenavir + ritonavir	Ciclosporin	Fosamprenavir increases plasma concentration of ciclosporin.
Fosamprenavir + ritonavir	Ergot alkaloids	Increased risk of ergotism when fosamprenavir given with ergotamine and methysergide (avoid concomitant use)
Fosamprenavir + ritonavir	Lipid-regulators, atorvastatin	Possible increased risk of myopathy when fosamprenavir given with atorvastatin
Fosamprenavir + ritonavir	Rosuvastatin	Possible increased risk of myopathy when fosamprenavir given with rosuvastatin (avoid concomitant use)
Fosamprenavir + ritonavir	Simvastatin	Possible increased risk of myopathy when fosamprenavir given with simvastatin (avoid concomitant use)
Fosamprenavir + ritonavir	Sildenafil	Fosamprenavir possibly increases plasma concentration of sildenafil.
Fosamprenavir + ritonavir	Tacrolimus	Fosamprenavir increases plasma concentration of tacrolimus.
Fosamprenavir + ritonavir	Vardenafil	Fosamprenavir possibly increases plasma concentration of vardenafil.
Fosamprenavir + ritonavir	Antivirals, lamivudine	Avoid concomitant use.
Fosamprenavir + ritonavir	Furosemide	See Diuretics.
Furazolidone	Amitriptyline	Psychosis reported when

		furazolidone given with amitriptyline
Furazolidone	Omeprazole	Rarely omeprazole reduces the blood concentration of furazolidone. Other proton pump inhibitors act toward furazolidone the same way as omeprazole.
Furazolidone	Alcohol	During and after treatment with furazolidone avoid use of alcohol.
Furosemide	Acetazolamide	Increased risk of hypokalemia
Furosemide	Alcohol	Enhanced hypotensive effect
Furosemide	Amikacine*	Increased risk of ototoxicity
Furosemide	Amitriptyline	Increased risk of postural hypotension
Furosemide	Amlodpine	Enhanced hypotensive effect
Furosemide	Amphotericin B	Increased risk of hypokalemia
Furosemide	Atenolol	Enhanced hypotensive effect
Furosemide	Carbamazepine	Increased risk of hyponatremia
Furosemide	Ceftazidime	May enhance nephrotoxicity of ceftazidime
Furosemide	Ceftriaxone	May enhance nephrotoxicity of ceftriaxone
Furosemide	Chlorpromazine	Increased risk of hyponatraemia
Furosemide	Clomipramine	Increased risk of postural hypotension
Furosemide	Clonazepam	Hypotensive effects may increase
Furosemide	Contraceptives, oral	Antagonism of diuretic effect by estrogens
Furosemide	Dexamethasone	Antagonism of diuretic effect; increased risk of hypokalaemia
Furosemide	Diazepam	Enhanced hypotensive effect
Furosemide	Digoxin*	Hypokalaemia caused by furosemide increases cardiac toxicity of digoxin.
Furosemide	Enalapril*	Enhanced hypotensive effect
Furosemide	Ether, anesthetic	Hypotensive effects may increase
Furosemide	Fluphenazine	Enhanced hypotensive effect

Furosemide	Gentamicin*	Increased risk of ototoxicity
Furosemide	Glibenclamide	Antagonism of hypoglycemic effect
Furosemide	Glyceryl trinitrate	Enhanced hypotensive effect
Furosemide	Halothane	Enhanced hypotensive effect
Furosemide	Hydralazine	Enhanced hypotensive effect
Furosemide	Hydrochlorothiazide	Increased risk of hypokalemia
Furosemide	Hydrocortisone	Antagonism of diuretic effect; increased risk of hypokalemia
Furosemide	Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Furosemide	Insulins	Antagonism of hypoglycemic effect
Furosemide	Isosorbide dinitrate	Enhanced hypotensive effect
Furosemide	Ketamine	Enhanced hypotensive effect
Furosemide	Levodopa	Enhanced hypotensive effect
Furosemide	Lidocaine*	Action of lidocaine antagonized by hypokalemia caused by furosemide (interaction less likely when lidocaine used topically)
Furosemide	Metformin	Antagonism of hypoglycemic effect
Furosemide	Methyldopa	Enhanced hypotensive effect
Furosemide	Nifedipine	Enhanced hypotensive effect
Furosemide	Nitrous oxide	Enhanced hypotensive effect
Furosemide	Prednisolone	Antagonism of diuretic effect; increased risk of hypokalemia
Furosemide	Propranolol	Enhanced hypotensive effect
Furosemide	Quinidine*	Cardiac toxicity of quinidine increased by hypokalaemia caused by furosemide
Furosemide	Salbutamol	Increased risk of hypokalemia with high doses of salbutamol
Furosemide	Sodium nitroprusside	Enhanced hypotensive effect
Furosemide	Streptomycin*	Increased risk of ototoxicity
Furosemide	Theophylline	Enhanced hypotensive effect
Furosemide	Thiopental	Enhanced hypotensive effect
Furosemide	Timolol	Enhanced hypotensive effect

Furosemide	Vancomycin*	Increased risk of ototoxicity
Furosemide	Verapamil	Enhanced hypotensive effect
Gentamicin	Amphotericin B	Increased risk of nephrotoxicity
Gentamicin	Capreomycin	Increased risk of nephrotoxicity and ototoxicity
Gentamicin	Ciclosporin*	Increased risk of nephrotoxicity
Gentamicin	Digoxin	Possibly increased plasma concentration of digoxin
Gentamicin	Furosemide*	Increased risk of ototoxicity
Gentamicin	Neostigmine*	Antagonism of effect of neostigmine
Gentamicin	Polygeline	Enhanced nephrotoxicity
Gentamicin	Pyridostigmine*	Antagonism of effect of pyridostigmine
Gentamicin	Suxamethonium*	Enhanced muscle relaxant effect
Gentamicin	Vancomycin	Increased risk of nephrotoxicity and ototoxicity
Gentamicin	Vecuronium*	Enhanced muscle relaxant effect
Glibenclamide	Alcohol	Enhanced hypoglycemic effect
Glibenclamide	Atenolol	Enhanced hypoglycemic effect
Glibenclamide	Chloramphenicol*	Atenolol may mask warning signs of hypoglycaemia such as tremor.
Glibenclamide	Chlorpromazine	Possible antagonism of hypoglycemic effect
Glibenclamide	Ciprofloxacin	Possibly enhanced effect of glibenclamide
Glibenclamide	Contraceptives, oral	Antagonism of hypoglycaemic effect by estrogens and progestogens
Glibenclamide	Dexamethasone	Antagonism of hypoglycemic effect
Glibenclamide	Enalapril	Hypoglycemic effect possibly enhanced
Glibenclamide	Fluconazole*	Plasma concentration of glibenclamide increased
Glibenclamide	Fluphenazine	Possible antagonism of hypoglycaemic effect
Glibenclamide	Furosemide	Antagonism of hypoglycemic effect
Glibenclamide	Hydrochlorothiazide	Antagonism of hypoglycemic effect

Glibenclamide	Hydrocortisone	Antagonism of hypoglycemic effect
Glibenclamide	Ibuprofen*	Possibly enhanced effect of glibenclamide
Glibenclamide	Levonorgestrel	Antagonism of hypoglycemic effect
Glibenclamide	Medroxyprogesterone	Antagonism of hypoglycemic effect
Glibenclamide	Norethisterone	Antagonism of hypoglycemic effect
Glibenclamide	Prednisolone	Antagonism of hypoglycemic effect
Glibenclamide	Propranolol	Propranolol may mask warning signs of hypoglycaemia such as tremor.
Glibenclamide	Rifampicin*	Possibly accelerated metabolism (reduced effect) of glibenclamide
Glibenclamide	Silver sulfadiazine	Effect of glibenclamide rarely enhanced
Glibenclamide	Sulfadiazine	Effect of glibenclamide rarely enhanced
Glibenclamide	Sulfadoxine + pyrimethamine	Effect of glibenclamide rarely enhanced
Glibenclamide	Sulfamethoxazole + trimethoprim	Effect of glibenclamide rarely enhanced
Glibenclamide	Testosterone	Hypoglycemic effect possibly enhanced
Glibenclamide	Timolol	Timolol may mask warning signs of hypoglycemia such as tremor.
Glibenclamide	Trimethoprim	Effects of glibenclamide rarely enhanced
Glibenclamide	Warfarin*	Possibly enhanced hypoglycemic effect and changes to anticoagulant effect
Glyceryl trinitrate	Acetazolamide	Enhanced hypotensive effect
Glyceryl trinitrate	Alcohol	Enhanced hypotensive effect
Glyceryl trinitrate	Amiloride	Enhanced hypotensive effect
Glyceryl trinitrate	Amitriptyline	Reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)

Glyceryl trinitrate	Amlodipine	Enhanced hypotensive effect
Glyceryl trinitrate	Atenolol	Enhanced hypotensive effect
Glyceryl trinitrate	Atropine	Possibly reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Glyceryl trinitrate	Biperiden	Possibly reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Glyceryl trinitrate	Chlorpromazine	Enhanced hypotensive effect
Glyceryl trinitrate	Clomipramine	Reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Glyceryl trinitrate	Clonazepam	Increase hypotensive effects
Glyceryl trinitrate	Contraceptives, oral	Antagonism of hypotensive effect by estrogens
Glyceryl trinitrate	Dexamethasone	Antagonism of hypotensive effect
Glyceryl trinitrate	Diazepam	Enhanced hypotensive effect
Glyceryl trinitrate	Enalapril	Enhanced hypotensive effect
Glyceryl trinitrate	Ether, anesthetic	Increase hypotensive effects
Glyceryl trinitrate	Fluphenazine	Enhanced hypotensive effect
Glyceryl trinitrate	Furosemide	Enhanced hypotensive effect
Glyceryl trinitrate	Halothane	Enhanced hypotensive effect
Glyceryl trinitrate	Heparin*	Anticoagulant effect reduced by infusion of glyceryl trinitrate
Glyceryl trinitrate	Hydralazine	Enhanced hypotensive effect
Glyceryl trinitrate	Hydrochlorothiazide	Enhanced hypotensive effect
Glyceryl trinitrate	Hydrocortisone	Antagonism of hypotensive effect
Glyceryl trinitrate	Ibuprofen	Antagonism of hypotensive effect
Glyceryl trinitrate	Ketamine	Enhanced hypotensive effect
Glyceryl trinitrate	Levodopa	Enhanced hypotensive effect
Glyceryl trinitrate	Methyldopa	Enhanced hypotensive effect
Glyceryl trinitrate	Nifedipine	Enhanced hypotensive effect
Glyceryl trinitrate	Nitrous oxide	Enhanced hypotensive effect

Glyceryl trinitrate	Prednisolone	Antagonism of hypotensive effect
Glyceryl trinitrate	Propranolol	Enhanced hypotensive effect
Glyceryl trinitrate	Sodium nitroprusside	Enhanced hypotensive effect
Glyceryl trinitrate	Spironolactone	Enhanced hypotensive effect
Glyceryl trinitrate	Thiopental	Enhanced hypotensive effect
Glyceryl trinitrate	Timolol	Enhanced hypotensive effect
Glyceryl trinitrate	Verapamil	Enhanced hypotensive effect
Griseofulvin	Ciclosporin	Plasma ciclosporin concentration possibly reduced
Griseofulvin	Contraceptives, oral*	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Griseofulvin	Levonorgestrel*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Griseofulvin	Medroxyprogesterone*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Griseofulvin	Norethisterone*	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Griseofulvin	Phenobarbital	Reduced absorption of griseofulvin (reduced effect)
Griseofulvin	Warfarin*	Reduced anticoagulant effect
Haloperidol	Alcohol	Enhanced sedative effect
Haloperidol	Amitriptyline*	Increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
Haloperidol	Amlodipine	Enhanced hypotensive effect
Haloperidol	Atropine	Possibly reduced effects of haloperidol
Haloperidol	Biperiden	Possibly reduced effects of haloperidol

Haloperidol	Carbamazepine*	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
Haloperidol	Clomipramine*	Increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
Haloperidol	Clonazepam	Enhance sedative effect
Haloperidol	Codeine	Enhanced sedative and hypotensive effect
Haloperidol	Diazepam	Enhanced sedative effect
Haloperidol	Dopamine	Antagonism of hypertensive effect
Haloperidol	Enalapril	Enhanced hypotensive effect
Haloperidol	Ephedrine	Antagonism of hypertensive effect
Haloperidol	Epinephrine	Antagonism of hypertensive effect
Haloperidol	Ether, anesthetic	Enhance hypotensive effect
Haloperidol	Ethosuximide*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Haloperidol	Fluoxetine*	Plasma concentration of haloperidol increased
Haloperidol	Halothane*	Enhanced hypotensive effect
Haloperidol	Isoprenaline	Inhibit vasoconstrictive effect
Haloperidol	Ketamine*	Enhanced hypotensive effect
Haloperidol	Levodopa	Antagonism of effects of levodopa
Haloperidol	Methadone	Enhanced hypotensive and sedative effects
Haloperidol	Methyldopa	Enhanced hypotensive effect; increased risk of extrapyramidal effects
Haloperidol	Metoclopramide	Increased risk of extrapyramidal effects
Haloperidol	Morphine	Enhanced hypotensive and sedative effects
Haloperidol	Nifedipine	Enhanced hypotensive effect

Haloperidol	Nitrous oxide*	Enhanced hypotensive effect
Haloperidol	Phenobarbital*	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
Haloperidol	Phenytoin*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Haloperidol	Procainamide*	Increased risk of ventricular arrhythmias
Haloperidol	Quinidine*	Increased risk of ventricular arrhythmias
Haloperidol	Rifampicin*	Accelerated metabolism of haloperidol (reduced plasma haloperidol concentration)
Haloperidol	Ritonavir*	Plasma concentration possibly increased by ritonavir
Haloperidol	Thiopental*	Enhanced hypotensive effect
Haloperidol	Valproic acid*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Haloperidol	Verapamil	Enhanced hypotensive effect
Halothane	Acetazolamide	Enhanced hypotensive effect
Halothane	Amiloride	Enhanced hypotensive effect
Halothane	Amlodipine	Enhanced hypotensive effect
Halothane	Amitriptyline	Increased risk of arrhythmias and hypotension
Halothane	Atenolol	Enhanced hypotensive effect
Halothane	Chlorpromazine*	Enhanced hypotensive effect
Halothane	Clomipramine	Increased risk of arrhythmias and hypotension
Halothane	Clonazepam	Enhanced sedative effect
Halothane	Diazepam	Enhanced sedative effect
Halothane	Enalapril	Enhanced hypotensive effect
Halothane	Epinephrine*	Risk of arrhythmias

Halothane	Ergometrine	Reduced effect of ergometrine on parturient uterus
Halothane	Methylergometrine maleate	Enhanced hypotensive effect
Halothane	Fluphenazine*	Enhanced hypotensive effect
Halothane	Furosemide	Enhanced hypotensive effect
Halothane	Glyceryltrinitrate	Enhanced hypotensive effect
Halothane	Haloperidol*	Enhanced hypotensive effect
Halothane	Hydralazine	Enhanced hypotensive effect
Halothane	Hydrochlorothiazide	Enhanced hypotensive effect
Halothane	Isoniazid	Possible potentiation of isoniazid hepatotoxicity
Halothane	Isoprenaline	Risk of arrhythmias
Halothane	Isosorbide dinitrate	Enhanced hypotensive effect
Halothane	Levodopa*	Risk of arrhythmias
Halothane	Methyldopa	Enhanced hypotensive effect
Halothane	Nifedipine	Enhanced hypotensive effect
Halothane	Oxytocin	Oxytocic effect possibly reduced; enhanced hypotensive effect and risk of arrhythmias
Halothane	Propranolol	Enhanced hypotensive effect
Halothane	Sodium nitroprusside	Enhanced hypotensive effect
Halothane	Spironolactone	Enhanced hypotensive effect
Halothane	Suxamethonium	Enhanced effects of suxamethonium
Halothane	Theophylline	Risk of arrhythmias
Halothane	Timolol	Enhanced hypotensive effect
Halothane	Vancomycin	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
Halothane	Vecuronium	Enhanced effects of vecuronium
Halothane	Verapamil*	Enhanced hypotensive effect and AV delay
Heparin	Acetylsalicylic acid*	Enhanced anticoagulant effect of heparin
Heparin	Enalapril	Increased risk of hyperkalemia

Heparin	Glyceryl trinitrate*	Anticoagulant effect reduced by infusion of glyceryl trinitrate
Heparin	Ibuprofen	Possibly increased risk of bleeding
Hydralazine	Acetazolamide	Enhanced hypotensive effect
Hydralazine	Alcohol	Enhanced hypotensive effect
Hydralazine	Amiloride	Enhanced hypotensive effect
Hydralazine	Amitriptyline	Enhanced hypotensive effect
Hydralazine	Atenolol	Enhanced hypotensive effect
Hydralazine	Chlorpromazine	Enhanced hypotensive effect
Hydralazine	Contraceptives, oral	Antagonism of hypotensive effect by estrogens
Hydralazine	Clomipramine	Antagonism of hypotensive effect
Hydralazine	Clonazepam	Enhanced hypotensive effect
Hydralazine	Dexamethasone	Enhanced hypotensive effect
Hydralazine	Diazepam	Enhanced hypotensive effect
Hydralazine	Enalapril	Enhanced hypotensive effect
Hydralazine	Ether, anesthetic	Enhanced hypotensive effect
Hydralazine	Fluphenazine	Enhanced hypotensive effect
Hydralazine	Furosemide	Enhanced hypotensive effect
Hydralazine	Glyceryl trinitrate	Enhanced hypotensive effect
Hydralazine	Halothane	Enhanced hypotensive effect
Hydralazine	Hydrochlorothiazide	Enhanced hypotensive effect
Hydralazine	Hydrocortisone	Antagonism of hypotensive effect
Hydralazine	Ibuprofen	Antagonism of hypotensive effect
Hydralazine	Isosorbide dinitrate	Enhanced hypotensive effect
Hydralazine	Ketamine	Enhanced hypotensive effect
Hydralazine	Levodopa	Enhanced hypotensive effect
Hydralazine	Methyldopa	Enhanced hypotensive effect
Hydralazine	Nifedipine	Enhanced hypotensive effect
Hydralazine	Nitrous oxide	Enhanced hypotensive effect
Hydralazine	Prednisolone	Antagonism of hypotensive effect
Hydralazine	Propranolol	Enhanced hypotensive effect
Hydralazine	Sodium nitroprusside	Enhanced hypotensive effect
Hydralazine	Spironolactone	Enhanced hypotensive effect
Hydralazine	Thiopental	Enhanced hypotensive effect
Hydralazine	Timolol	Enhanced hypotensive effect

Hydralazine	Verapamil	Enhanced hypotensive effect
Hydrochlorothiazide	Acetazolamide	Increased risk of hypokalemia
Hydrochlorothiazide	Alcohol	Enhanced hypotensive effect
Hydrochlorothiazide	Allopurinol	Increased risk of hypersensitivity, especially in renal impairment
Hydrochlorothiazide	Amitriptyline	Increased risk of postural hypotension
Hydrochlorothiazide	Amlodipine	Enhanced hypotensive effect
Hydrochlorothiazide	Amphotericin B	Increased risk of hypokalemia
Hydrochlorothiazide	Atenolol	Enhanced hypotensive effect
Hydrochlorothiazide	Calcium salts	Increased risk of hypercalcemia
Hydrochlorothiazide	Carbamazepine	Increased risk of hypercalcemia
Hydrochlorothiazide	Chlorpromazine	Enhanced hypotensive effect
Hydrochlorothiazide	Clomipramine	Increased risk of postural hypotension
Hydrochlorothiazide	Clonazepam	Enhanced hypotensive effect
Hydrochlorothiazide	Contraceptives, oral	Antagonism of diuretic effect by estrogens
Hydrochlorothiazide	Dexamethasone	Antagonism of diuretic effect; increased risk of hypokalemia
Hydrochlorothiazide	Diazepam	Enhanced hypotensive effect
Hydrochlorothiazide	Digoxin*	Hypokalaemia caused by hydrochlorothiazide increases cardiac toxicity of digoxin
Hydrochlorothiazide	Enalapril*	Enhanced hypotensive effect
Hydrochlorothiazide	Ergocalciferol	Increased risk of hypercalcemia
Hydrochlorothiazide	Ether, anesthetic	Enhanced hypotensive effect
Hydrochlorothiazide	Fluconazole	Plasma concentration of fluconazole increased
Hydrochlorothiazide	Fluphenazine	Enhanced hypotensive effect
Hydrochlorothiazide	Furosemide	Increased risk of hypokalemia
Hydrochlorothiazide	Glibenclamide	Antagonism of hypoglycemic effect
Hydrochlorothiazide	Glyceryl trinitrate	Enhanced hypotensive effect
Hydrochlorothiazide	Halothane	Enhanced hypotensive effect
Hydrochlorothiazide	Hydralazine	Enhanced hypotensive effect
Hydrochlorothiazide	Hydrocortisone	Antagonism of diuretic effect;

		increased risk of hypokalaemia
Hydrochlorothiazide	Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Hydrochlorothiazide	Insulins	Antagonism of hypoglycemic effect
Hydrochlorothiazide	Isosorbide dinitrate	Enhanced hypotensive effect
Hydrochlorothiazide	Ketamine	Enhanced hypotensive effect
Hydrochlorothiazide	Levodopa	Enhanced hypotensive effect
Hydrochlorothiazide	Lidocaine*	Action of lidocaine antagonized by hypokalaemia caused by hydrochlorothiazide (interaction less likely when lidocaine used topically)
Hydrochlorothiazide	Metformin	Antagonism of hypoglycemic effect
Hydrochlorothiazide	Methyldopa	Enhanced hypotensive effect
Hydrochlorothiazide	Nifedipine	Enhanced hypotensive effect
Hydrochlorothiazide	Nitrous oxide	Enhanced hypotensive effect
Hydrochlorothiazide	Prednisolone	Antagonism of diuretic effect; increased risk of hypokalemia
Hydrochlorothiazide	Propranolol	Enhanced hypotensive effect
Hydrochlorothiazide	Quinidine*	Cardiac toxicity of quinidine increased by hypokalemia caused by hydrochlorothiazide
Hydrochlorothiazide	Salbutamol	Increased risk of hypokalemia with high doses of salbutamol
Hydrochlorothiazide	Sodium nitroprusside	Enhanced hypotensive effect
Hydrochlorothiazide	Theophylline	Increase risk of hypokalemia
Hydrochlorothiazide	Thiopental	Enhanced hypotensive effect
Hydrochlorothiazide	Timolol	Enhanced hypotensive effect
Hydrochlorothiazide	Verapamil	Enhanced hypotensive effect
Hydrocortisone	Note: Interactions do not generally apply to hydrocortisone used for topical application.	
Hydrocortisone	Acetazolamide	Increased risk of hypokalemia; antagonism of diuretic effect
Hydrocortisone	Acetyl salicylic acid	Increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma

		salicylate concentration
Hydrocortisone	Amiloride	Antagonism of diuretic effect
Hydrocortisone	Amlodpine	Antagonism of hypotensive effect
Hydrocortisone	Amphotericin B *	Increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions)
Hydrocortisone	Atenolol	Antagonism of hypotensive effect
Hydrocortisone	Carbamazepine *	Accelerated metabolism of hydrocortisone (reduced effect)
Hydrocortisone	Calcium salts	Reduced absorption of calcium salts
Hydrocortisone	Contraceptives, oral	Oral contraceptives containing estrogens increase plasma concentration of hydrocortisone
Hydrocortisone	Digoxin	Increased risk of hypokalemia
Hydrocortisone	Enalapril	Antagonism of hypotensive effect
Hydrocortisone	Erythromycin	Erythromycin possibly inhibits metabolism of hydrocortisone
Hydrocortisone	Furosemide	Antagonism of diuretic effect; increased risk of hypokalemia
Hydrocortisone	Glibenclamide	Antagonism of hypoglycemic effect
Hydrocortisone	Glyceryltrinitrate	Antagonism of hypotensive effect
Hydrocortisone	Hydralazine	Antagonism of hypotensive effect
Hydrocortisone	Hydrochlorothiazide	Antagonism of diuretic effect; increased risk of hypokalaemia
Hydrocortisone	Ibuprofen	Increased risk of gastrointestinal bleeding and ulceration
Hydrocortisone	Insulins	Antagonism of hypoglycemic effect
Hydrocortisone	Isosorbide dinitrate	Antagonism of hypotensive effect
Hydrocortisone	Levonorgestrel	Increase plasma concentration of hydrocortison
Hydrocortisone	Medroxyprogesterone	Increase plasma concentration of hydrocortison
Hydrocortisone	Metformin	Antagonism of hypoglycemic effect
Hydrocortisone	Methotrexate*	Increased risk of hematological

		toxicity
Hydrocortisone	Methyldopa	Antagonism of hypotensive effect
Hydrocortisone	Nifedipine	Antagonism of hypotensive effect
Hydrocortisone	Phenobarbital*	Metabolism of hydrocortisone accelerated (reduced effect)
Hydrocortisone	Phenytoin*	Metabolism of hydrocortisone accelerated (reduced effect)
Hydrocortisone	Propranolol	Antagonism of hypotensive effect
Hydrocortisone	Rifampicin*	Accelerated metabolism of hydrocortisone (reduced effect)
Hydrocortisone	Ritonavir	Plasma concentration possibly increased by ritonavir
Hydrocortisone	Salbutamol	Increased risk of hypokalemia if high doses of salbutamol given with hydrocortisone
Hydrocortisone	Sodium nitroprusside	Antagonism of hypotensive effect
Hydrocortisone	Spironolactone	Antagonism of diuretic effect
Hydrocortisone	Theophylline	Increase risk of hypokalemia
Hydrocortisone	Vaccine, live*	High doses of hydrocortisone impair immune response
Hydrocortisone	Verapamil	Antagonism of hypotensive effect
Hydrocortisone	Warfarin*	Anticoagulant effect possibly enhanced or reduced (high-dose hydrocortisone enhances anticoagulant effect)
Hydroxocobalamine	Chloramphenicol	Reduced hydroxocobalamin activity
Hyoscine	See Atropine.	
Ibuprofen	Acetazolamide	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Ibuprofen	Acetylsalicylic acid*	Avoid concomitant use (increased adverse effects); antiplatelet effect of acetylsalicylic acid possibly reduced
Ibuprofen	Amiloride	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic

		effect; possibly increased risk of hyperkalemia
Ibuprofen	Amlodipine	Antagonism of hypotensive effect
Ibuprofen	Atenolol	Antagonism of hypotensive effect
Ibuprofen	Ciclosporin*	Increased risk of nephrotoxicity
Ibuprofen	Ciprofloxacin*	Possibly increased risk of convulsions
Ibuprofen	Dexamethasone	Increased risk of gastrointestinal bleeding and ulceration
Ibuprofen	Digoxin	Possibly exacerbation of heart failure, reduced renal function, and increased plasma digoxin concentration
Ibuprofen	Enalapril	Antagonism of hypotensive effect, increased risk of renal impairment
Ibuprofen	Fluoxetine*	Increased risk of bleeding
Ibuprofen	Furosemide	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Ibuprofen	Glibenclamide*	Possibly enhanced effect of glibenclamide
Ibuprofen	Glyceryl trinitrate	Antagonism of hypotensive effect
Ibuprofen	Heparin	Possibly increased risk of bleeding
Ibuprofen	Hydralazine	Antagonism of hypotensive effect
Ibuprofen	Hydrochlorothiazide	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
Ibuprofen	Hydrocortisone	Increased risk of gastrointestinal bleeding and ulceration
Ibuprofen	Isosorbide dinitrate	Antagonism of hypotensive effect
Ibuprofen	Levofloxacin*	Possibly increased risk of convulsions
Ibuprofen	Methotrexate*	Excretion of methotrexate reduced (increased risk of toxicity)
Ibuprofen	Methyldopa	Antagonism of hypotensive effect
Ibuprofen	Nalidixic acid	Increased risk of convulsions

Ibuprofen	Mifepristone	Avoidance of ibuprofen advised by manufacturer of mifepristone
Ibuprofen	Nifedipine	Antagonism of hypotensive effect
Ibuprofen	Ofloxacin*	Possibly increased risk of convulsions
Ibuprofen	Phenytoin*	Effect of phenytoin possibly enhanced
Ibuprofen	Prednisolone	Increased risk of gastrointestinal bleeding and ulceration
Ibuprofen	Propranolol	Antagonism of hypotensive effect
Ibuprofen	Ritonavir	Plasma concentration possibly increased by ritonavir
Ibuprofen	Sodium nitroprusside	Antagonism of hypotensive effect
Ibuprofen	Spironolactone	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalemia
Ibuprofen	Verapamil	Antagonism of hypotensive effect
Ibuprofen	Warfarin*	Anticoagulant effect possibly enhanced
Ibuprofen	Zidovudine	Increased risk of hematological toxicity
Imipramine	Cimetidine	Inhibited metabolism of amitriptyline, imipramine, and nortriptyline (increased plasma concentration)
Imipramine	Moclobemide	Increase plasma concentration of moclobemide
Imipramine	Thyroid hormones	Effects of tricyclics enhanced by thyroid hormones
Imipramine	Thyroid hormones	Effects of amitriptyline and imipramine enhanced by thyroid hormones
Imipramine	Ulcer-healing drugs	Plasma concentration of tricyclics possibly increased by cimetidine
Imipramine	Propranolol	Increased plasma concentration of imipramine

Imipramine	Thyroid hormones	Effects of amitriptyline and imipramine enhanced by thyroid hormones effects of tricyclics possibly enhanced by thyroid hormones)
Immunoglobulin (human) anti-D	Vaccine, live*	Avoid use of live virus vaccine during <i>4 weeks before</i> or during <i>3 months after</i> injection of anti-D immunoglobulin (impairment of immune response) but rubella vaccine (either as MMR or as single-antigen rubella vaccine) may be given at the same time as anti-D immunoglobulin.
Immunoglobulin, human, normal	Vaccine, live*	Avoid use of live vaccine during <i>3 weeks before</i> or during <i>3 months after</i> injection of human normal immunoglobulin (impairment of immune response).
Indinavir	Carbamazepine	Possibly reduced plasma indinavir concentration
Indinavir	Dexamethasone	Possibly reduced plasma indinavir concentration
Indinavir	Efavirenz	Efavirenz reduces plasma concentration of indinavir
Indinavir	Ergotamine	Increase risk of ergotism (avoid concomitant use)
Indinavir	Nelfinavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
Indinavir	Nevirapine	Nevirapine reduces plasma concentration of indinavir
Indinavir	Phenobarbital*	Plasma concentration of indinavir possibly reduced
Indinavir	Phenytoin	Plasma indinavir concentration possibly reduced
Indinavir	Rifampicin*	Metabolism accelerated by

		rifampicin (plasma indinavir concentration reduced—avoid concomitant use)
Indinavir	Ritonavir	Ritonavir increases plasma concentration of indinavir
Indinavir	Saquinavir	Indinavir increases plasma concentration of saquinavir
Indinavir	Simvastatin*	Increased risk of myopathy
Insulins	Alcohol	Enhanced hypoglycaemic effect
Insulins	Atenolol	Enhanced hypoglycemic effect; atenolol may mask warning signs of hypoglycemia such as tremor
Insulins	Contraceptives, oral	Antagonism of hypoglycemic effect by estrogens and progestogens
Insulins	Dexamethasone	Antagonism of hypoglycemic effect
Insulins	Enalapril	Hypoglycaemic effect possibly enhanced
Insulins	Furosemide	Antagonism of hypoglycemic effect
Insulins	Hydrochlorothiazide	Antagonism of hypoglycemic effect
Insulins	Hydrocortisone	Antagonism of hypoglycemic effect
Insulins	Levonorgestrel	Antagonism of hypoglycemic effect
Insulins	Medroxyprogesterone	Antagonism of hypoglycemic effect
Insulins	Nifedipine	Occasionally impaired glucose tolerance
Insulins	Norethisterone	Antagonism of hypoglycemic effect
Insulins	Prednisolone	Antagonism of hypoglycemic effect
Insulins	Propranolol	Enhanced hypoglycaemic effect; propranolol may mask warning signs of hypoglycemia such as tremor
Insulins	Testosterone	Hypoglycaemic effect possibly enhanced
Insulins	Timolol	Enhanced hypoglycaemic effect; timolol may mask warning signs of hypoglycemia such as tremor
Iron (see Ferrous salts)		

Isoflurane	See Anesthetics, general. ACE inhibitors	Enhanced hypotensive effect in concomitant use of general anesthetics and ACE inhibitors
Isoflurane	Neurdrenergic	Enhanced hypotensive effect in concomitant use of general anesthetics and Adrenergic Neuron
Isoflurane	Alpha-blockers	Enhanced hypotensive effect in concomitant use of general anesthetics and alpha-blockers
Isoflurane	Analgesics	Enhanced effect of thiopental with aspirin
Isoflurane	Opioid analgesics	Possibly intravenous effect of general anesthetics increase with volatile liquid, opioid analgesics
Isoflurane	Diazoxide	Enhanced hypotensive effect in concomitant use of general anesthetics and diazoxide
Isoflurane	Diuretics	Enhanced hypotensive effect in concomitant use of general anesthetics and diuretics
Isoflurane	Levodopa	Concomitant use of general anesthetics with levodopa increase risk of arrhythmia.
Isoflurane	Methyldopa	Enhanced hypotensive effect in concomitant use of general anesthetics and diazoxide
Isoflurane	Metoclopramide	Enhanced effect of thiopental with metoclopramide
Isoflurane	Nitrates	Enhanced hypotensive effect in concomitant use of general anesthetics and nitrates
Isoniazid	Amitriptyline	Increased plasma concentration of isoniazid
Isoniazid	Antacids (Aluminium hydroxide; magnesium hydroxide)	Reduced absorption of isoniazid
Isoniazid	Carbamazepine*	Increased plasma carbamazepine

		concentration (also isoniazid hepatotoxicity possibly increased)
Isoniazid	Diazepam	Metabolism of diazepam inhibited
Isoniazid	Ether, anesthetic	May increase hepatotoxicity effects of isoniazid
Isoniazid	Ethosuximide*	Metabolism of ethosuximide inhibited (increased plasma ethosuximide concentration and risk of toxicity)
Isoniazid	Halothane	Possible potentiation of isoniazid hepatotoxicity
Isoniazid	Ketamine	Possible potentiation of isoniazid hepatotoxicity
Isoniazid	Nitrous oxide	Possible potentiation of isoniazid hepatotoxicity
Isoniazid	P-aminosalicylic acid	Increased plasma concentration of isoniazid
Isoniazid	Phenytoin*	Metabolism of phenytoin inhibited (enhanced effect)
Isoniazid	Theophylline	May increase plasma concentration of theophylline
Isoniazid	Thiopental	Possible potentiation of isoniazid hepatotoxicity
Isophane insulin (see Insulins)		
Isosorbide dinitrate	Acetazolamide	Enhanced hypotensive effect
Isosorbide dinitrate	Alcohol	Enhanced hypotensive effect
Isosorbide dinitrate	Amitriptyline	Reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Isosorbide dinitrate	Atenolol	Enhanced hypotensive effect
Isosorbide dinitrate	Atropine	Possibly reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Isosorbide dinitrate	Biperiden	Possibly reduced effect of sublingual isosorbide dinitrate

		tablets (failure to dissolve under the tongue owing to dry mouth)
Isosorbide dinitrate	Chlorpromazine	Enhanced hypotensive effect
Isosorbide dinitrate	Clomipramine	Reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
Isosorbide dinitrate	Clonazepam	Enhance hypotensive effect
Isosorbide dinitrate	Contraceptives, oral	Antagonism of hypotensive effect by estrogens
Isosorbide dinitrate	Dexamethasone	Antagonism of hypotensive effect
Isosorbide dinitrate	Diazepam	Enhanced hypotensive effect
Isosorbide dinitrate	Enalapril	Enhanced hypotensive effect
Isosorbide dinitrate	Ether, anesthetic	Enhance hypotensive effect
Isosorbide dinitrate	Fluphenazine	Enhanced hypotensive effect
Isosorbide dinitrate	Furosemide	Enhanced hypotensive effect
Isosorbide dinitrate	Halothane	Enhanced hypotensive effect
Isosorbide dinitrate	Hydralazine	Enhanced hypotensive effect
Isosorbide dinitrate	Hydrochlorothiazide	Enhanced hypotensive effect
Isosorbide dinitrate	Hydrocortizone	Antagonism of hypotensive effect
Isosorbide dinitrate	Ibuprofen	Antagonism of hypotensive effect
Isosorbide dinitrate	Ketamine	Enhanced hypotensive effect
Isosorbide dinitrate	Levodopa	Enhanced hypotensive effect
Isosorbide dinitrate	Methyldopa	Enhanced hypotensive effect
Isosorbide dinitrate	Nifedipine	Enhanced hypotensive effect
Isosorbide dinitrate	Nitrous oxide	Enhanced hypotensive effect
Isosorbide dinitrate	Prednisolone	Antagonism of hypotensive effect
Isosorbide dinitrate	Propranolol	Enhanced hypotensive effect
Isosorbide dinitrate	Sodium nitroprusside	Enhanced hypotensive effect
Isosorbide dinitrate	Spironolactone	Enhanced hypotensive effect
Isosorbide dinitrate	Thiopental	Enhanced hypotensive effect
Isosorbide dinitrate	Timolol	Enhanced hypotensive effect
Isosorbide dinitrate	Verapamil	Enhanced hypotensive effect
Ketamine	Acetazolamide	Enhanced hypotensive effect
Ketamine	Amiloride	Enhanced hypotensive effect
Ketamine	Amlodipine	Enhanced hypotensive effect

Ketamine	Amitriptyline	Increased risk of arrhythmias and hypotension
Ketamine	Atenolol	Enhanced hypotensive effect
Ketamine	Chlorpromazine*	Enhanced hypotensive effect
Ketamine	Clomipramine	Increased risk of arrhythmias and hypotension
Ketamine	Clonazepam	Enhanced sedative effect
Ketamine	Diazepam	Enhanced sedative effect
Ketamine	Enalapril	Enhanced hypotensive effect
Ketamine	Fluphenazine*	Enhanced hypotensive effect
Ketamine	Furosemide	Enhanced hypotensive effect
Ketamine	Glyceryl trinitrate	Enhanced hypotensive effect
Ketamine	Haloperidol*	Enhanced hypotensive effect
Ketamine	Hydralazine	Enhanced hypotensive effect
Ketamine	Hydrochlorothiazide	Enhanced hypotensive effect
Ketamine	Isoniazid	Possible potentiation of isoniazid hepatotoxicity
Ketamine	Isosorbide dinitrate	Enhanced hypotensive effect
Ketamine	Methyldopa	Enhanced hypotensive effect
Ketamine	Nifedipine	Enhanced hypotensive effect
Ketamine	Propranolol	Enhanced hypotensive effect
Ketamine	Sodium nitroprusside	Enhanced hypotensive effect
Ketamine	Spironolactone	Enhanced hypotensive effect
Ketamine	Theophylline	Risk of convulsion
Ketamine	Timolol	Enhanced hypotensive effect
Ketamine	Vancomycin	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin.
Ketamine	Verapamil*	Enhanced hypotensive effect and AV delay
Lamivudine	Sulfamethoxazole + trimethoprim	Plasma concentration of lamivudine increased (avoid concomitant use of high-dose sulfamethoxazole + trimethoprim)
Lamivudine	Emtricitabine	No information available; manufacturer advises avoid

		concomitant use.
Lactulose	Anticoagulants, coumarin	Lactulose may enhance anticoagulant effect of coumarin
Levodopa + carbidopa	Acetazolamide	Enhanced hypotensive effect
Levodopa + carbidopa	Amiloride	Enhanced hypotensive effect
Levodopa + Carbidopa	Amlodipine	Enhanced hypotensive effect
Levodopa + Carbidopa	Atenolol	Enhanced hypotensive effect
Levodopa + Carbidopa	Atropine	Absorption of levodopa possibly reduced
Levodopa + Carbidopa	Biperiden	Absorption of levodopa possibly reduced
Levodopa + Carbidopa	Chlorpromazine	Antagonism of effects of levodopa
Levodopa + Carbidopa	Diazepam	Possibly antagonism of levodopa effects
Levodopa + Carbidopa	Enalapril	Enhanced hypotensive effect
Levodopa + Carbidopa	Ferrous salts	Absorption of levodopa may be reduced by oral ferrous salts
Levodopa + carbidopa	Fluphenazine	Antagonism of effects of levodopa
Levodopa + carbidopa	Furosemide	Enhanced hypotensive effect
Levodopa + carbidopa	Glyceryl trinitrate	Enhanced hypotensive effect
Levodopa + carbidopa	Haloperidol	Antagonism of effects of levodopa
Levodopa + carbidopa	Halothane*	Risk of arrhythmias
Levodopa + carbidopa	Hydralazine	Enhanced hypotensive effect
Levodopa + carbidopa	Hydrochlorothiazide	Enhanced hypotensive effect
Levodopa + carbidopa	Isosorbide dinitrate	Enhanced hypotensive effect
Levodopa + carbidopa	Methyldopa	Enhanced hypotensive effect; antagonism of anti-Parkinsonism effect
Levodopa+ Carbidopa	Nifedipine	Enhanced hypotensive effect
Levodopa+ Carbidopa	Phenytoin	Possibly reduced effects of levodopa
Levodopa+ Carbidopa	Propranolol	Enhanced hypotensive effect
Levodopa+ Carbidopa	Pyridoxine	Antagonism of effects of levodopa

		unless carbidopa also given
Levodopa + carbidopa	Sodium nitroprusside	Enhanced hypotensive effect
Levodopa + carbidopa	Spironolactone	Enhanced hypotensive effect
Levodopa + carbidopa	Timolol	Enhanced hypotensive effect
Levodopa + carbidopa	Verapamil	Enhanced hypotensive effect
Levonorgestrel	See also Contraceptives, oral.	
Levonorgestrel	Carbamazepine*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Levonorgestrel	Ciclosporin*	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
Levonorgestrel	Glibenclamide	Antagonism of hypoglycemic effect
Levonorgestrel	Griseofulvin*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Levonorgestrel	Insulins	Antagonism of hypoglycemic effect
Levonorgestrel	Metformin	Antagonism of hypoglycemic effect
Levonorgestrel	Nelfinavir	Contraceptive effect of levonorgestrel possibly reduced
Levonorgestrel	Nevirapine*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Levonorgestrel	Phenobarbital*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Levonorgestrel	Phenytoin*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Levonorgestrel	Rifampicin*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Levonorgestrel	Ritonavir*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)

Levonorgestrel	Warfarin*	Antagonism of anticoagulant effect
Levothyroxine	Amitriptyline	Enhanced effects of amitriptyline
Levothyroxine	Calcium salts	Reduced absorption of levothyroxine
Levothyroxine	Carbamazepine	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
Levothyroxine	Clomipramine	Possibly enhanced effects of clomipramine
Levothyroxine	Ferrous salts	Absorption of levothyroxine reduced by oral ferrous salts
Levothyroxine	Phenobarbital	Metabolism of levothyroxine accelerated (may increase levothyroxine requirements in hypothyroidism)
Levothyroxine	Phenytoin	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism); plasma concentration of phenytoin possibly increased
Levothyroxine	Propranolol	Accelerated metabolism of propranolol (reduced effect)
Levothyroxine	Rifampicin	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
Levothyroxine	Warfarin*	Enhanced anticoagulant effect
Lidocaine	Note: Interactions less likely when lidocaine is used topically	
Lidocaine	Acetazolamide*	Hypokalemia caused by acetazolamide antagonizes action of lidocaine
Lidocaine	Atenolol *	Increased myocardial depression
Lidocaine	Bupivacaine	Increased myocardial depression
Lidocaine	Furosemide*	Action of lidocaine antagonized by hypokalemia caused by furosemide

Lidocaine	Hydrochlorothiazide *	Action of lidocaine antagonized by hypokalemia caused by furosemide
Lidocaine	Lopinavir	Possibly increased plasma concentration of lidocaine
Lidocaine	Procainamide*	Increased myocardial depression
Lidocaine	Propranolol*	Increased myocardial depression; increased risk of lidocaine toxicity
Lidocaine	Quinidine*	Increased myocardial depression
Lidocaine	Suxamethonium	Neuromuscular blockade enhanced and prolonged
Lidocaine	Timolol*	Increased myocardial depression
Lidocaine	Verapamil*	Increased myocardial depression
Lopinavir	Carbamazepine*	Possibly reduced plasma lopinavir concentration
Lopinavir	Chlorphenamine	Possibly increased plasma concentration of chlorphenamine
Lopinavir	Dexamethasone*	Possibly reduced plasma lopinavir concentration
Lopinavir	Efavirenz*	Plasma concentration of lopinavir reduced
Lopinavir	Lidocaine	Possibly increased plasma concentration of lidocaine
Lopinavir	Nelfinavir	Plasma concentration of lopinavir reduced; plasma
Lopinavir	Phenobarbital*	Plasma concentration of lopinavir possibly reduced
Lopinavir	Phenytoin	Plasma lopinavir concentration possibly reduced
Lopinavir	Nevirapine	Plasma concentration of lopinavir possibly reduced
Lopinavir	Rifampicin*	Reduced plasma concentration of lopinavir (avoid concomitant use)
Lopinavir	Saquinavir	Increased plasma concentration of saquinavir
Lopinavir	Simvastatin*	Increased risk of myopathy
Lopinavir	Tenofovir*	Plasma concentration of tenofovir

		increased
Lopinavir	Magnesium hydroxide	See antacids.
Magnesium (parenteral)	Nifedipine*	Profound hypotension reported with nifedipine and intravenous magnesium sulfate in pre-eclampsia
Magnesium (parenteral)	Suxamethonium	Enhanced muscle relaxant effect
Magnesium (parenteral)	Vecuronium	Enhanced muscle relaxant effect
Magnesium sulfate	See Magnesium (parenteral).	
Measles vaccine	See Vaccine, live.	
Mebendazole	Carbamazepine	Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection)
Mebendazole	Phenobarbital	Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection)
Mebendazole	Phenytoin	Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection)
Medroxyprogesterone	Carbamazepine*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Medroxyprogesterone	Ciclosporin*	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
Medroxyprogesterone	Dexamethasone	Increase plasma concentration of dexamethasone
Medroxyprogesterone	Glibenclamide	Antagonism of hypoglycemic effect
Medroxyprogesterone	Griseofulvin*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for

		contraception)
Medroxyprogesterone	Hydrocortisone	Increase plasma concentration of hydrocortisone
Medroxyprogesterone	Insulins	Antagonism of hypoglycemic effect
Medroxyprogesterone	Metformin	Antagonism of hypoglycemic effect
Medroxyprogesterone	Nelfinavir	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Medroxyprogesterone	Nevirapine*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Medroxyprogesterone	Phenobarbital*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Medroxyprogesterone	Phenytoin*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Medroxyprogesterone	Prednisolone	Accelerated metabolism of medroxyprogesterone
Medroxyprogesterone	Rifampicin*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Medroxyprogesterone	Ritonavir*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)

Medroxyprogesterone	Warfarin*	Antagonism of anticoagulant effect
Metformin	Alcohol	Enhanced hypoglycemic effect; increased risk of lactic acidosis
Metformin	Atenolol	Atenolol may mask warning signs of hypoglycaemia such as tremor
Metformin	Contraceptives, oral	Antagonism of hypoglycemic effect by estrogens and progestogens
Metformin	Dexamethazone	Antagonism of hypoglycemic effect
Metformin	Enalapril	Hypoglycaemic effect possibly enhanced
Metformin	Furosemide	Antagonism of hypoglycemic effect
Metformin	Hydrochlorothiazide	Antagonism of hypoglycaemic effect
Metformin	Hydrocortisone	Antagonism of hypoglycemic effect
Metformin	Levonogestrel	Antagonism of hypoglycemic effect
Metformin	Medroxyprogesterone	Antagonism of hypoglycemic effect
Metformin	Norethistrone	Antagonism of hypoglycemic effect
Metformin	Prednisolone	Antagonism of hypoglycemic effect
Metformin	Propranolol	Propranolol may mask warning signs of hypoglycaemia such as tremor.
Metformin	Testosterone	Hypoglycemic effect possibly enhanced
Metformin	Timolol	Timolol may mask warning signs of hypoglycemia such as tremor.
Methadone		See Morphine.
Methotrexate	Acetylsalicylic acid*	Reduced excretion of methotrexate (increased risk of toxicity)
Methotrexate	Amoxicillin	Reduced excretion of methotrexate (increased risk of toxicity)
Methotrexate	Ampicillin	Reduced excretion of methotrexate (increased risk of toxicity)
Methotrexate	Benzylpencillin	Reduced excretion of methotrexate (increased risk of toxicity)
Methotrexate	Ciclosporin*	Increased toxicity
Methotrexate	Dexamethasone*	Increased risk of hematological toxicity

Methotrexate	Doxycycline	Increased risk of hematological toxicity
Methotrexate	Hydrocortisone*	Increased risk of hematological toxicity
Methotrexate	Ibuprofen*	Excretion of methotrexate reduced (increased risk of toxicity)
Methotrexate	Nitrous oxide*	Increased antifolate effect (avoid concomitant use)
Methotrexate	Phenoxymethylpenicillin	Reduced excretion of methotrexate (increased risk of toxicity)
Methotrexate	Phenytoin*	Reduced absorption of phenytoin; antifolate effect of methotrexate increased
Methotrexate	Prednisolone*	Increased risk of hematological toxicity
Methotrexate	Pyrimethamine*	Antifolate effect of methotrexate increased
Methotrexate	Sulfadiazine	Risk of methotrexate toxicity increased
Methotrexate	Sulfadoxine* + pyrimethamine	Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased
Methotrexate	Sulfamethoxazole* + trimethoprim	Antifolate effect of methotrexate increased (avoid concomitant use); risk of methotrexate toxicity increased
Methotrexate	Trimethoprim*	Antifolate effect of methotrexate increased (avoid concomitant use)
Methotrexate	Vaccine, live	Avoid use of live vaccines with methotrexate (impairment of immune response)
Methyldopa	Acetazolamide	Enhanced hypotensive effect
Methyldopa	Alcohol	Enhanced hypotensive effect
Methyldopa	Amiloride	Enhanced hypotensive effect
Methyldopa	Amlodipine	Enhanced hypotensive effect
Methyldopa	Amitriptyline	Enhanced hypotensive effect

Methyldopa	Atenolol	Enhanced hypotensive effect
Methyldopa	Chlorpromazine	Enhanced hypotensive effect; increased risk of extrapyramidal effects
Methyldopa	Clomipramine	Enhanced hypotensive effect
Methyldopa	Clonazepam	Enhanced hypotensive effect
Methyldopa	Contraceptives, oral	Antagonism of hypotensive effect by estrogens
Methyldopa	Dexamethasone	Antagonism of hypotensive effect
Methyldopa	Diazepam	Enhanced hypotensive effect
Methyldopa	Enalapril	Enhanced hypotensive effect
Methyldopa	Ether, anesthetic	Enhanced hypotensive effect
Methyldopa	Ferrous salts	Oral ferrous salts reduce hypotensive effect of methyldopa
Methyldopa	Fluphenazine	Enhanced hypotensive effect; increased risk of extrapyramidal effects
Methyldopa	Furosemide	Enhanced hypotensive effect
Methyldopa	Glyceryl trinitrate	Enhanced hypotensive effect
Methyldopa	Haloperidol	Enhanced hypotensive effect; increased risk of extrapyramidal effects
Methyldopa	Halothane	Enhanced hypotensive effect
Methyldopa	Hydralazine	Enhanced hypotensive effect
Methyldopa	Hydrochlorothiazide	Enhanced hypotensive effect
Methyldopa	Hydrocortisone	Antagonism of hypotensive effect
Methyldopa	Ibuprofen	Antagonism of hypotensive effect
Methyldopa	Isosorbide dinitrate	Enhanced hypotensive effect
Methyldopa	Ketamine	Enhanced hypotensive effect
Methyldopa	Levodopa	Enhanced hypotensive effect; antagonism of anti-Parkinsonism effect
Methyldopa	Nifedipine	Enhanced hypotensive effect
Methyldopa	Nitrous oxide	Enhanced hypotensive effect
Methyldopa	Prednisolone	Antagonism of hypotensive effect
Methyldopa	Propranolol	Enhanced hypotensive effect

Methyldopa	Salbutamol*	Acute hypotension reported with salbutamol infusion
Methyldopa	Sodium nitroprusside	Enhanced hypotensive effect
Methyldopa	Spironolactone	Enhanced hypotensive effect
Methyldopa	Thiopental	Enhanced hypotensive effect
Methyldopa	Timolol	Enhanced hypotensive effect
Methyldopa	Verapamil	Enhanced hypotensive effect
Metoclopramide	Acetylsalicylic acid	Enhanced effect of acetylsalicylic acid (increased rate of absorption)
Metoclopramide	Atropine	Antagonism of effects of metoclopramide on gastrointestinal activity
Metoclopramide	Biperiden	Antagonism of effects of metoclopramide on gastrointestinal activity
Metoclopramide	Chlorpromazine	Increased risk of extrapyramidal effects
Metoclopramide	Ciclosporin*	Plasma ciclosporin concentration increased
Metoclopramide	Codeine	Antagonism of effect of metoclopramide on gastrointestinal activity
Metoclopramide	Fluphenazine	Increased risk of extrapyramidal effects
Metoclopramide	Haloperidol	Increased risk of extrapyramidal effects
Metoclopramide	Morphine	Antagonism of effect of metoclopramide on gastrointestinal activity
Metoclopramide	Paracetamol	Increased absorption of paracetamol
Metoclopramide	Suxamethonium	Enhanced effects of suxamethonium
Metoprolol	ACE inhibitor	Enhance hypotensive effect
Metoprolol	Adrenergic neuron blockers	Enhance hypotensive effect
Metoprolol	Alcohol	Enhance hypotensive effect

Metoprolol	Alpha-blocker	Enhance hypotensive effect
Metoprolol	General anesthetics	Enhance hypotensive effect
Metoprolol	NSAIDs	NSAIDs antagonize hypotensive effect
Metoprolol	Angiotensin-II receptor antagonists	Enhance hypotensive effect
Metoprolol	Anti-arrhythmia medicine	Increased risk of myocardial depression and when given with amiodarone increased risk of bradycardia and atrioventricular AV block
Metoprolol	Oral antidiabetics and insulin	When beta-blockers are given with antidiabetic medicines the signs of hypoglycemic risks such as tremor may be masked, also hypoglycemic effect of insulin enhanced by beta-blockers
Metoprolol	Meflaquine	Enhance risk of bradycardia
Metoprolol	Phenothiazine	Enhanced hypotensive effect
Metoprolol	Sedative and hypnotics	Enhanced hypotensive effect when beta-blockers given with anxiolytics and hypnotics
Metoprolol	Calcium-channel blockers	Enhanced hypotensive effect when beta-blockers given with calcium-channel blockers
Metoprolol	Cardiac glycosides	Increased risk of AV block and bradycardia
Metoprolol	Corticosteroids	Hypotensive effect of beta-blockers antagonised by corticosteroids
Metoprolol	Diazoxide	Enhanced hypotensive effect
Metoprolol	Diuretics	Enhanced hypotensive effect
Metoprolol	Levodopa	Enhanced hypotensive effect when beta-blockers given with levodopa
Metoprolol	Ergot alkaloids ergotamine	Increased peripheral vasoconstriction when beta-blockers given with ergotamine
Metoprolol	Methyldopa	Enhanced hypotensive effect when

		beta-blockers given with methyl dopa
Metoprolol	Nitrates	Enhanced hypotensive effect
Metoprolol	Estrogens	Hypotensive effect of beta-blockers antagonized by estrogens
Metoprolol	Pilocarpine	Increased risk of arrhythmias
Metoprolol	Adrenaline	Possibly increased risk of severe hypertension
Metoprolol	Cimetidine	Increase plasma concentration of metoprolol
Metoprolol	Vasodilator: antihypertensive, hydralazine, minoxidil, or sodium nitroprusside	Enhanced hypotensive effect when beta-blockers given with hydralazine, minoxidil, or sodium nitroprusside
Metronidazole	Alcohol	Disulfiram-like reaction
Metronidazole	Contraceptives, oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
Metronidazole	Fluorouracil	Metabolism of fluorouracil inhibited (increased toxicity)
Metronidazole	Phenobarbital	Metabolism of metronidazole accelerated (reduced plasma concentration)
Metronidazole	Phenytoin*	Metabolism of phenytoin inhibited (increased plasma phenytoin concentration)
Metronidazole	Warfarin*	Enhanced anticoagulant effect
Midazolam	Theophylline	Increased theophylline metabolism (decreased effect)
Morphine	Alcohol	Enhanced sedative and hypotensive effects
Morphine	Amitriptyline	Possibly increased sedation
Morphine	Chlorpromazine	Enhanced sedative and hypotensive effects
Morphine	Ciprofloxacin	Manufacturer of ciprofloxacin advises avoid premedication with morphine (reduced plasma ciprofloxacin concentration) when

		ciprofloxacin used for surgical prophylaxis.
Morphine	Clomipramine	Possibly increased sedation
Morphine	Clonazepam	Enhanced sedative effect
Morphine	Diazepam	Enhanced sedative effect
Morphine	Fluphenazine	Enhanced sedative and hypotensive effects
Morphine	Haloperidol	Enhanced sedative and hypotensive effects
Morphine	Metoclopramide	Antagonism of effect of metoclopramide on gastrointestinal activity
Morphine	Ritonavir*	Ritonavir possibly increases plasma concentration of morphine.
Moxifloxacin	Antacids	Decreased absorption of quinolones
Moxifloxacin	Anti-arrhythmics	Increase risk of ventricular arrhythmias by concomitant use of levofloxacin and moxifloxacin with amiodaron (avoid concomitant use)
Moxifloxacin	Antimalarials	Increased risk of ventricular arrhythmias by concomitant use of moxifloxacin chloroquine hydroxychloroqui • (avoid concomitant use)
Moxifloxacin	Analgesics	Increased risk of convulsion on concomitant use of quinolones with NSAIDs
Moxifloxacin	Tricyclics	Increase risk of ventricular arrhythmias by concomitant use of moxifloxacin with tricyclics (avoid concomitant use)
Moxifloxacin	Beta-blockers	Increase risk of ventricular arrhythmias by concomitant use of moxifloxacin with beta-blockers (avoid concomitant use)
Moxifloxacin	Ciclosporin	Increased risk of nephrotoxicity on concomitant use of quinolones and

		ciclospoin
Nalidixic acid	Ciclosporin	Enhanced nephrotoxic effects
Nalidixic acid	Ibuprofen	May enhance risk of convulsions
Nalidixic acid	Theophylline	May enhance risk of convulsions
Nalidixic acid	Warfarin	Increased anticoagulant effect
Naphazoline	Monoamine oxidase inhibitors (MAOIs)	Since naphazoline is absorbed via nasal mucosa, interactions may occur after topical use.
Nelfinavir	Carbamazepine	Possibly reduced plasma nelfinavir concentration
Nelfinavir	Ciclosporin*	Possibly increased plasma ciclosporin concentration
Nelfinavir	Contraceptives,* oral	Accelerated metabolism of estrogens (reduced contraceptive effect); nelfinavir possibly reduces contraceptive effect of progestogens.
Nelfinavir	Ergotamine	Increased risk of ergotism (avoid concomitant use)
Nelfinavir	Indinavir	Combination may lead to increased plasma concentration of either drug (or both drugs).
Nelfinavir	Levonorgestrel	Contraceptive effect of levonorgestrel possibly reduced
Nelfinavir	Medroxyprogesterone	Accelerate metabolism of medroxyprogesterone
Nelfinavir	Norethisterone*	Possibly reduced contraceptive effect
Nelfinavir	Phenobarbital*	Plasma concentration of nelfinavir possibly reduced
Nelfinavir	Phenytoin	Reduced plasma phenytoin concentration
Nelfinavir	Quinidine*	Increased risk of ventricular arrhythmias (avoid concomitant use)
Nelfinavir	Rifampicin*	Plasma concentration of nelfinavir significantly reduced (avoid concomitant use)

Nelfinavir	Ritonavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
Nelfinavir	Saquinavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
Nelfinavir	Simvastatin *	Increased risk of myopathy
Neostigmine	Atropine	Antagonism of effect of neostigmine
Neostigmine	Amikacin*	Antagonism of effect of neostigmine
Neostigmine	Biperiden	Antagonism of effect of neostigmine
Neostigmine	Chloroquine	Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine.
Neostigmine	Clindamycin	Antagonism of effect of neostigmine
Neostigmine	Gentamicin*	Antagonism of effect of neostigmine
Neostigmine	Paromomycin*	Possibly antagonism
Neostigmine	Procainamide	Antagonism of effect of neostigmine
Neostigmine	Propranolol	Antagonism of effect of neostigmine
Neostigmine	Quinidine	Antagonism of effect of neostigmine
Neostigmine	Streptomycin*	Antagonism of effect of neostigmine
Neostigmine	Suxamethonium	Effect of suxamethonium enhanced
Neostigmine	Vecuronium	Antagonism of muscle relaxant effect
Nevirapine	Contraceptives, oral	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Nevirapine	Efavirenz	Plasma efavirenz concentration reduced
Nevirapine	Fluconazole	Increased plasma concentration of nevirapine
Nevirapine	Indinavir	Nevirapine reduces plasma concentration of indinavir.
Nevirapine	Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)

Nevirapine	Lopinavir	Plasma concentration of lopinavir possibly reduced
Nevirapine	Medroxyprogesterone*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Nevirapine	Methadone	Possibly reduced plasma concentration of methadone
Nevirapine	Norethisterone*	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Nevirapine	Rifampicin*	Reduced plasma concentration of nevirapine (avoid concomitant use)
Nevirapine	Saquinavir	Plasma concentration of saquinavir reduced
Nevirapine	Warfarin*	Enhanced or reduced anticoagulant effect
Nifedipine	Acetazolamide	Enhanced hypotensive effect
Nifedipine	Alcohol	Enhanced hypotensive effect
Nifedipine	Amiloride	Enhanced hypotensive effect
Nifedipine	Atenolol,* and beta-blockers*	Enhanced hypotensive effect; possibly severe hypotension and heart failure
Nifedipine	Carbamazepine	Probably reduced effect of nifedipine
Nifedipine	Chlorpromazine	Enhanced hypotensive effect
Nifedipine	Ciclosporin	Possibly increased plasma nifedipine concentration (increased risk of adverse effects such as gingival hyperplasia)
Nifedipine	Clonazepam	Enhance hypotensive effect
Nifedipine	Contraceptives, oral	Antagonism of hypotensive effect by estrogens
Nifedipine	Dexamethasone	Antagonism of hypotensive effect
Nifedipine	Diazepam	Enhanced hypotensive effect

Nifedipine	Digoxin*	Possibly increased plasma concentration of digoxin
Nifedipine	Enalapril	Enhanced hypotensive effect
Nifedipine	Ether, anesthetic	Enhanced hypotensive effect
Nifedipine	Fluphenazine	Enhanced hypotensive effect
Nifedipine	Furosemide	Enhanced hypotensive effect
Nifedipine	Glyceryl trinitrate	Enhanced hypotensive effect
Nifedipine	Grapefruit juice	Increased plasma nifedipine concentration
Nifedipine	Haloperidol	Enhanced hypotensive effect
Nifedipine	Halothane	Enhanced hypotensive effect
Nifedipine	Hydralazine	Enhanced hypotensive effect
Nifedipine	Hydrochlorothiazide	Enhanced hypotensive effect
Nifedipine	Hydrocortisone	Antagonism of hypotensive effect
Nifedipine	Ibuprofen	Antagonism of hypotensive effect
Nifedipine	Insulins	Occasionally impaired glucose tolerance
Nifedipine	Isosorbide dinitrate	Enhanced hypotensive effect
Nifedipine	Ketamine	Enhanced hypotensive effect
Nifedipine	Levodopa	Enhanced hypotensive effect
Nifedipine	Magnesium* (parenteral)	Profound hypotension reported with nifedipine and intravenous magnesium sulfate in pre-eclampsia
Nifedipine	Methyldopa	Enhanced hypotensive effect
Nifedipine	Nitrous oxide	Enhanced hypotensive effect
Nifedipine	Phenobarbital*	Effect of nifedipine probably reduced
Nifedipine	Phenytoin*	Probably reduced effect of nifedipine
Nifedipine	Prednisolone	Antagonism of hypotensive effect
Nifedipine	Propranolol*	Enhanced hypotensive effect; possibly severe hypotension and heart failure
Nifedipine	Quinidine	Reduced plasma quinidine concentration
Nifedipine	Ritonavir*	Plasma concentration possibly

		increased by ritonavir
Nifedipine	Rifampicin*	Accelerated metabolism of nifedipine (plasma concentration significantly reduced)
Nifedipine	Sodium nitroprusside	Enhanced hypotensive effect
Nifedipine	Spironolactone	Enhanced hypotensive effect
Nifedipine	Theophylline	Enhanced hypotensive effect
Nifedipine	Thiopental	Enhanced hypotensive effect
Nifedipine	Timolol*	Enhanced hypotensive effect; possibly severe hypotension and heart failure
Nifedipine	Vecuronium	Enhanced muscle relaxant effect
Nifedipine	Vincristine	Possibly reduced metabolism of vincristine
Norethisterone (<i>see also</i> Contraceptives, oral)		
Norethisterone	Carbamazepine*	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Norethisterone	Ciclosporin*	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
Norethisterone	Dexamethasone	Increase plasma concentration of dexamethasone
Norethisterone	Glibenclamide	Antagonism of hypoglycemic effect
Norethisterone	Griseofulvin*	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Norethisterone	Hydrocortisone	Increase plasma concentration of hydrocortisone
Norethisterone	Insulins	Antagonism of hypoglycaemic effect
Norethisterone	Metformin	Antagonism of hypoglycaemic effect
Norethisterone	Nelfinavir*	Possibly reduced contraceptive effect
Norethisterone	Nevirapine*	Accelerated metabolism of norethisterone (reduced

		contraceptive effect)
Norethisterone	Phenobarbital*	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Norethisterone	Phenytoin*	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Norethisterone	Prednisolone	Increase plasma concentration of prednisolone
Norethisterone	Warfarin*	Antagonism of anticoagulant effect
Norgestrel	See Progestogens	
Nortriptyline	See Amitriptyline	
Omeprazole	Anticoagulants, coumarins	Esomeprazole, omeprazole, and pantoprazole possibly enhance anticoagulant effect of coumarins.
Omeprazole	Antipsychotics clozapine	Omeprazole possibly reduces plasma concentration of clozapine.
Omeprazole	Nelfinavir	Omeprazole reduces plasma concentration of nelfinavir.
Omeprazole	Raltegravir	Omeprazole reduces plasma concentration of raltegravir.
Omeprazole	Anxiolytics and hypnotics Diazepam	Omeprazole and esomeprazole antagonize metabolism of diazepam (increase plasma concentration).
Omeprazole	Ciclosporin	Omeprazole may affect on plasma concentration of ciclosporin.
Omeprazole	Cilostazol	Plasma concentration of cilostazole increase by omeprazole.
Omeprazole	Clopidogrel	Omeprazole and esomeprazole antagonize antiplatelet effect of clopidogrel.
Omeprazole	Methotrexate	Omeprazole may reduce excretion of methotrexate (increased risk of toxicity).
Opium tincture		Consider caution when opium tinctures are used with other medicines.

Oxygen	Bleomycin	Serious pulmonary toxicity in patients exposed to conventional oxygen concentrations during anaesthesia
Oxytocin	Epinephrine	Risk of hypertension due to enhanced vasopressor effect of epinephrine
Oxytocin	Ephedrine	Risk of hypertension due to enhanced vasopressor effect of ephedrine
Oxytocin	Ether, anesthetic	Oxytotic effect possibly reduced; enhanced hypotensive effect and risk of arrhythmias
Oxytocin	Halothane	Oxytotic effect possibly reduced; enhanced hypotensive effect and risk of arrhythmias
Paracetamol	Alcohol	Increase risk of liver impairment by regular consumption of high volumes of alcohol
Paracetamol	Metoclopramide	Increased absorption of paracetamol (increase effect)
Paracetamol	Warfarin	Prolonged regular use of paracetamol possibly enhances anticoagulant effect of warfarin.
Penicillamine	Antacids (aluminium hydroxide; magnesium hydroxide)	Reduced absorption of penicillamine
Penicillamine	Digoxin	Plasma concentration of digoxin possibly reduced
Penicillamine	Ferrous salts	Oral ferrous salts reduce absorption of penicillamine.
Penicillamine	Ibuprofen	Possibly increased risk of nephrotoxicity
Penicillamine	Zinc sulfate	Absorption of penicillamine and zinc sulfate reduced
Pethidine		See morphine and analgesic opiates.

Phenobarbital	Abacavir	Plasma concentration of abacavir possibly reduced
Phenobarbital	Acetazolamide	Increased risk of osteomalacia
Phenobarbital	Alcohol	Enhanced sedative effect
Phenobarbital	Amitriptyline*	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of amitriptyline possibly accelerated (reduced plasma concentration)
Phenobarbital	Amlodipine*	Probably reduced effect of amlodipine
Phenobarbital	Carbamazepine*	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of carbamazepine reduced
Phenobarbital	Chloramphenicol*	Metabolism of chloramphenicol accelerated (reduced plasma chloramphenicol concentration)
Phenobarbital	Chlorpromazine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Phenobarbital	Ciclosporin*	Metabolism of ciclosporin accelerated (reduced effect)
Phenobarbital	Clomipramine*	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of clomipramine possibly accelerated (reduced plasma concentration)
Phenobarbital	Clonazepam	May increase toxicity without increase in its anticonvulsive effect; plasma concentration of clonazepam reduced
Phenobarbital	Contraceptives, oral*	Metabolism of estrogens and progestogens accelerated (reduced contraceptive effect)
Phenobarbital	Dexamethasone*	Metabolism of dexamethasone accelerated (reduced effect)

Phenobarbital	Doxycycline	Metabolism of doxycycline accelerated (reduced plasma concentration)
Phenobarbital	Ergocalciferol	Ergocalciferol requirements possibly increased
Phenobarbital	Ethosuximide	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of ethosuximide possibly reduced
Phenobarbital	Fluoxetine	Antagonism of anticonvulsive effect (convulsive threshold lowered)
Phenobarbital	Fluphenazine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Phenobarbital	Folic acid and Folinic acid	Plasma concentration of phenobarbital possibly reduced
Phenobarbital	Griseofulvin	Reduced absorption of griseofulvin (reduced effect)
Phenobarbital	Haloperidol*	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
Phenobarbital	Hydrocortisone*	Metabolism of hydrocortisone accelerated (reduced effect)
Phenobarbital	Indinavir*	Plasma concentration of indinavir possibly reduced
Phenobarbital	Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Phenobarbital	Levothyroxine*	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
Phenobarbital	Lopinavir*	Plasma concentration of lopinavir possibly reduced
Phenobarbital	Mebendazole	Reduced plasma mebendazole

		concentration (possibly increased mebendazole dose in tissue infection)
Phenobarbital	Medroxyprogesterone*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Phenobarbital	Metronidazole	Metabolism of metronidazole accelerated (reduced plasma concentration)
Phenobarbital	Nelfinavir*	Plasma concentration of nelfinavir possibly reduced
Phenobarbital	Nifedipine*	Effect of nifedipine probably reduced
Phenobarbital	Norethisterone *	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Phenobarbital	Phenytoin	May enhance toxicity without corresponding increase in anti-epileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of phenobarbital often raised
Phenobarbital	Prednisolone*	Metabolism of prednisolone accelerated (reduced effect)
Phenobarbital	Quinidine	Metabolism of quinidine accelerated (reduced plasma concentration)
Phenobarbital	Saquinavir*	Plasma concentration of saquinavir possibly reduced
Phenobarbital	Theophylline	Metabolism of theophylline accelerated (reduced plasma concentration)
Phenobarbital	Valproic acid	Possibly enhanced toxicity without corresponding increase in anti-epileptic effect; plasma

		concentration of valproic acid reduced; plasma phenobarbital concentration increased
Phenobarbital	Verapamil*	Effect of verapamil probably reduced
Phenobarbital	Warfarin*	Metabolism of warfarin accelerated (reduced anticoagulant effect)
Phenoxymethylpenicillin	Methotrexate	Reduced excretion of methotrexate (increased risk of toxicity)
Phenoxymethylpenicillin	Contraceptives, oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
Phenytoin	Abacavir	Plasma concentration of abacavir possibly reduced
Phenytoin	Acetazolamide	Increased risk of osteomalacia
Phenytoin	Acetylsalicylic acid	Enhancement of effect of phenytoin
Phenytoin	Alcohol	Plasma phenytoin concentration reduced with regular large amounts of alcohol
Phenytoin	Amitriptyline*	Antagonism of anticonvulsant effect (convulsive threshold lowered); possibly reduced plasma amitriptyline concentration
Phenytoin	Amlodipine	Probably reduced effect of amlodipine
Phenytoin	Antacids (aluminium hydroxide; magnesium hydroxide)	Reduced absorption of phenytoin
Phenytoin	Azathioprine	Possibly reduced absorption of phenytoin
Phenytoin	Carbamazepine*	Possibly enhanced toxicity without corresponding increase in anti-epileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of carbamazepine often lowered

Phenytoin	Chloramphenicol*	Plasma phenytoin concentration increased (increased risk of toxicity)
Phenytoin	Chloroquine	Possibly increased risk of convulsions
Phenytoin	Chlorpromazine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Phenytoin	Ciclosporin*	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
Phenytoin	Ciprofloxacin	Plasma phenytoin concentration can be increased or decreased by ciprofloxacin
Phenytoin	Clomipramine*	Antagonism of anticonvulsant effect (convulsive threshold lowered); possibly reduced plasma clomipramine concentration
Phenytoin	Clonazepam	May increase toxicity without increase in anticonvulsive effect; plasma concentration of clonazepam reduced
Phenytoin	Contraceptives, oral*	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Phenytoin	Cyclophosphamide	Possibly reduced absorption of phenytoin
Phenytoin	Cytarabine	Reduced absorption of phenytoin
Phenytoin	Dexamethasone*	Metabolism of dexamethasone accelerated (reduced effect)
Phenytoin	Diazepam	Plasma phenytoin concentration possibly increased or decreased by diazepam
Phenytoin	Digoxin	Plasma concentration of digoxin possibly reduced
Phenytoin	Doxorubicin	Possibly reduced absorption of phenytoin
Phenytoin	Doxycycline	Increased metabolism of doxycycline (reduced plasma

		concentration)
Phenytoin	Ergocalciferol	Ergocalciferol requirements possibly increased
Phenytoin	Ethosuximide*	Possibly enhanced toxicity without corresponding increase in anti-epileptic effect; plasma concentration of phenytoin possibly increased; plasma concentration of ethosuximide possibly reduced
Phenytoin	Fluconazole*	Plasma concentration of phenytoin increased (consider reducing dose of phenytoin)
Phenytoin	Fluoxetine *	Plasma concentration of phenytoin increased
Phenytoin	Fluorouracil	Metabolism of phenytoin possibly inhibited (increased risk of toxicity)
Phenytoin	Fluphenazine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Phenytoin	Folic acid and folinic acid	Plasma phenytoin concentration possibly reduced
Phenytoin	Haloperidol*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Phenytoin	Hydrocortisone *	Metabolism of hydrocortisone accelerated (reduced effect)
Phenytoin	Ibuprofen*	Effect of phenytoin possibly enhanced
Phenytoin	Indinavir	Plasma indinavir concentration possibly reduced
Phenytoin	Isoniazid*	Metabolism of phenytoin inhibited (enhanced effect)
Phenytoin	Levamisole	Plasma phenytoin concentration possibly increased
Phenytoin	Levodopa	Possibly reduced effects of levodopa
Phenytoin	Levonorgestrel *	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)

Phenytoin	Levothyroxine	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism); plasma concentration of phenytoin possibly increased
Phenytoin	Lopinavir	Plasma lopinavir concentration possibly reduced
Phenytoin	Mebendazole	Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection)
Phenytoin	Medroxyprogesterone*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable edroxyprogesterone acetate used for contraception)
Phenytoin	Mercaptopurine	Reduced absorption of phenytoin
Phenytoin	Methadone	Accelerated metabolism of methadone (reduced effect and risk of withdrawal symptoms)
Phenytoin	Methotrexate	Possibly reduced absorption of phenytoin
Phenytoin	Metronidazole*	Metabolism of phenytoin inhibited (increased plasma phenytoin concentration)
Phenytoin	Nelfinavir	Reduced plasma phenytoin concentration
Phenytoin	Nifedipine*	Probably reduced effect of nifedipine
Phenytoin	Norethisterone *	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Phenytoin	Phenobarbital	Possibly enhanced toxicity without corresponding increase in anti-epileptic effect; plasma concentration of phenytoin often

		lowered but may be raised; plasma concentration of phenobarbital often raised
Phenytoin	Praziquantel	Plasma praziquantel concentration reduced
Phenytoin	Prednisolone*	Metabolism of prednisolone accelerated (reduced effect)
Phenytoin	Procarbazine	Reduced absorption of phenytoin
Phenytoin	Pyrimethamine*	Antagonism of anticonvulsant effect; increased antifolate effect
Phenytoin	Quinidine*	Accelerated metabolism of quinidine (reduced plasma quinidine concentration)
Phenytoin	Rifampicin*	Accelerated metabolism of phenytoin (reduced plasma concentration)
Phenytoin	Saquinavir	Plasma saquinavir concentration possibly reduced
Phenytoin	Silver sulfadiazine	Possibly increased plasma concentration of phenytoin
Phenytoin	Sulfadiazine	Plasma phenytoin concentration possibly increased
Phenytoin	Sulfadoxine* + pyrimethamine	Plasma phenytoin concentration possibly increased; increased antifolate effect
Phenytoin	Sulfamethoxazole* + trimethoprim	Antifolate effect and plasma phenytoin concentration increased
Phenytoin	Theophylline	Accelerate metabolism of theophylline (plasma concentration of both theophylline and phenytoin may be reduced)
Phenytoin	Trimethoprim*	Antifolate effect and plasma phenytoin concentration increased
Phenytoin	Vaccine, influenza	Enhanced effect of phenytoin
Phenytoin	Valproic acid	Possible enhanced toxicity without corresponding increase in anti-epileptic effect; plasma

		concentration of valproic acid reduced; plasma concentration of phenytoin increased or possibly reduced
Phenytoin	Vecuronium	Antagonism of muscle relaxant effect (accelerated recovery from neuromuscular blockade)
Phenytoin	Verapamil	Reduced effect of verapamil
Phenytoin	Warfarin*	Accelerated metabolism of warfarin (possibility of reduced anticoagulant effect, but enhancement also reported)
Phenytoin	Zidovudine	Plasma phenytoin concentration increased or decreased by zidovudine
Phytomenadione	Warfarin *	Antagonism of anticoagulant effect
Pilocarpine	Atenolol	Increased risk of arrhythmias
Pilocarpine	Atropine	Antagonism of effects of pilocarpine
Pilocarpine	Biperiden	Antagonism of effects of pilocarpine
Pilocarpine	Propranolol	Increased risk of arrhythmias
Pilocarpine	Timolol	Increased risk of arrhythmias
Poliomyelitis, Vaccine (oral)	See Vaccine, live	
Potassium salts	Amiloride*	Increased risk of hyperkalemia
Potassium salts	Ciclosporin*	Increased risk of hyperkalemia
Potassium salts	Enalapril*	Increased risk of severe hyperkalaemia
Potassium salts	Spironolactone and other potassium-sparing diuretics*	Risk of hyperkalemia
Prednisolone	Acetazolamide	Increased risk of hypokalemia; antagonism of diuretic effect
Prednisolone	Acetylsalicylic acid	Increased risk of gastrointestinal bleeding and ulceration; prednisolone reduces plasma salicylate concentration
Prednisolone	Amiloride	Antagonism of diuretic effect

Prednisolone	Amlodipine	Antagonism of hypotensive effect
Prednisolone	Amphotericin B *	Increased risk of hypokalemia (avoid concomitant use unless prednisolone needed to control reactions)
Prednisolone	Atenolol	Antagonism of hypotensive effect
Prednisolone	Calcium salts	Reduced absorption of calcium salts
Prednisolone	Carbamazepine *	Accelerated metabolism of prednisolone (reduced effect)
Prednisolone	Ciclosporin	Increased plasma concentration of prednisolone
Prednisolone	Contraceptives, oral	Oral contraceptives containing estrogens increase plasma concentration of prednisolone
Prednisolone	Digoxin	Increased risk of hypokaaemia
Prednisolone	Enalapril	Antagonism of hypotensive effect
Prednisolone	Erythromycin	Erythromycin possibly inhibits metabolism of prednisolone
Prednisolone	Furosemide	Antagonism of diuretic effect; increased risk of hypokalaemia
Prednisolone	Glibenclamide	Antagonism of hypoglycemic effect
Prednisolone	Glyceryl trinitrate	Antagonism of hypotensive effect
Prednisolone	Hydralazine	Antagonism of hypotensive effect
Prednisolone	Hydrochlorothiazide	Antagonism of diuretic effect; increased risk of hypokalaemia
Prednisolone	Ibuprofen	Increased risk of gastrointestinal bleeding and ulceration
Prednisolone	Insulins	Antagonism of hypoglycemic effect
Prednisolone	Isosorbide dinitrate	Antagonism of hypotensive effect
Prednisolone	Levonorgestrel	Increase plasma concentration of prednisolone
Prednisolone	Medroxyprogesterone	Increased plasma concentration of prednisolone
Prednisolone	Metformin	Antagonism of hypoglycemic effect
Prednisolone	Methotrexate*	Increased risk of hematological toxicity

Prednisolone	Methyldopa	Antagonism of hypotensive effect
Prednisolone	Nifedipine	Antagonism of hypotensive effect
Prednisolone	Norethisterone	Increase plasma concentration of prednisolone
Prednisolone	Phenobarbital*	Metabolism of prednisolone accelerated (reduced effect)
Prednisolone	Phenytoin*	Metabolism of prednisolone accelerated (reduced effect)
Prednisolone	Propranolol	Antagonism of hypotensive effect
Prednisolone	Rifampicin*	Accelerated metabolism of prednisolone (reduced effect)
Prednisolone	Ritonavir	Plasma concentration possibly increased by ritonavir
Prednisolone	Salbutamol	Increased risk of hypokalemia if high doses of salbutamol given with prednisolone
Prednisolone	Sodium nitroprusside	Antagonism of hypotensive effect
Prednisolone	Spironolactone	Antagonism of diuretic effect
Prednisolone	Theophylline	Increased risk of hypokalemia
Prednisolone	Vaccine, live*	High doses of prednisolone impair immune response; avoid use of live vaccines with prednisolone
Prednisolone	Verapamil	Antagonism of hypotensive effect
Prednisolone	Warfarin*	Anticoagulant effect possibly enhanced or reduced (high-dose prednisolone enhances anticoagulant effect)
Procainamide	Amitriptyline*	Increased risk of ventricular arrhythmias
Procainamide	Atenolol*	Increased myocardial depression
Procainamide	Bupivacaine	Increased myocardial depression
Procainamide	Chlorpromazine*	Increased risk of ventricular arrhythmias
Procainamide	Clomipramin*	Increased risk of ventricular arrhythmias
Procainamide	Fluphenazine*	Increased risk of ventricular

		arrhythmias
Procainamide	Haloperidol*	Increased risk of ventricular arrhythmias
Procainamide	Lidocaine*	Increased myocardial depression (interaction less likely when lidocaine used topically)
Procainamide	Neostigmine	Antagonism of effect of neostigmine
Procainamide	Propranolol*	Increased risk of myocardial depression
Procainamide	Pyridostigmine	Antagonism of effect of pyridostigmine
Procainamide	Quinidine*	Increased myocardial depression
Procainamide	Sulfamethoxazole + trimethoprim	Increased plasma procainamide concentration
Procainamide	Suxamethonium*	Enhanced muscle relaxant effect
Procainamide	Timolol*	Increased myocardial depression
Procainamide	Trimethoprim	Increased plasma procainamide concentration
Procainamide	Vecuronium*	Enhanced muscle relaxant effect
Procaine benzylpenicillin	See Benzylpenicillin	
Promethazine	Alcohol	Enhanced sedative effect
Promethazine	Amitriptyline	Increased antimuscarinic and sedative effects
Promethazine	Atropine	Increased risk of antimuscarinic adverse effects
Promethazine	Biperiden	Increased risk of antimuscarinic adverse effects
Promethazine	Clomipramine	Increased antimuscarinic and sedative effects
Promethazine	Clonazepam	Enhanced sedative effect
Promethazine	Diazepam	Enhanced sedative effect
Propofol	Suxamethonium	Increase myocardia depression and bradycardia, avoid concomitant use of propofol and suxamethonium
Propranolol	Acetazolamide	Enhanced hypotensive effect
Propranolol	Alcohol	Enhanced hypotensive effect

Propranolol	Amiloride	Enhanced hypotensive effect
Propranolol	Amlodipine	Enhanced hypotensive effect
Propranolol	Bupivacaine*	Increased risk of bupivacaine toxicity
Propranolol	Chlorpromazine*	Concomitant administration may increase plasma concentration of both drugs; enhanced hypotensive effect
Propranolol	Clonazepam	Enhanced hypotensive effect
Propranolol	Contraceptives, oral	Antagonism of hypotensive effect by estrogens
Propranolol	Dexamethasone	Antagonism of hypotensive effect
Propranolol	Diazepam	Enhanced hypotensive effect
Propranolol	Digoxin	Increased risk of AV block and bradycardia
Propranolol	Enalapril	Enhanced hypotensive effect
Propranolol	Epinephrine*	Severe hypertension
Propranolol	Ergotamine	Increase peripheral vasoconstriction
Propranolol	Ether, anesthetic	Enhanced hypotensive effect
Propranolol	Fluphenazine	Enhanced hypotensive effect
Propranolol	Furosemide	Enhanced hypotensive effect
Propranolol	Glibenclamide	Propranolol may mask warning signs of hypoglycaemia such as tremor.
Propranolol	Glyceryl trinitrate	Enhanced hypotensive effect
Propranolol	Halothane	Enhanced hypotensive effect
Propranolol	Hydralazine	Enhanced hypotensive effect
Propranolol	Hydrochlorothiazide	Enhanced hypotensive effect
Propranolol	Hydrocortisone	Antagonism of hypotensive effect
Propranolol	Ibuprofen	Antagonism of hypotensive effect
Propranolol	Insulins	Enhanced hypoglycemic effect; propranolol may mask warning signs of hypoglycaemia such as tremor
Propranolol	Isosorbide dinitrate	Enhanced hypotensive effect
Propranolol	Ketamine	Enhanced hypotensive effect

Propranolol	Levodopa	Enhanced hypotensive effect
Propranolol	Levothyroxine	Accelerate propranolol metabolism (reduced effect)
Propranolol	Lidocaine*	Increased myocardial depression; increased risk of lidocaine toxicity (interaction less likely when lidocaine used topically)
Propranolol	Metformin	Propranolol may mask warning signs of hypoglycaemia such as tremor
Propranolol	Methyldopa	Enhanced hypotensive effect
Propranolol	Neostigmine	Antagonism of effect of neostigmine
Propranolol	Nifedipine*	Enhanced hypotensive effect; possibly severe hypotension and heart failure
Propranolol	Nitrous oxide	Enhanced hypotensive effect
Propranolol	Pilocarpine	Increased risk of arrhythmias
Propranolol	Prednisolone	Antagonism of hypotensive effect
Propranolol	Procainamide*	Increased risk of myocardial depression
Propranolol	Pyridostigmine	Antagonism of effect of pyridostigmine
Propranolol	Quinidine*	Increased myocardial depression
Propranolol	Rifampicin	Metabolism of propranolol accelerated (significantly reduced plasma concentration)
Propranolol	Sodium nitroprusside	Enhanced hypotensive effect
Propranolol	Spironolacton	Enhanced hypotensive effect
Propranolol	Suxamethonium	Enhanced muscle relaxant effect
Propranolol	Thiopental	Enhanced hypotensive effect
Propranolol	Vecuronium	Enhanced muscle relaxant effect
Propranolol	Verapamil*	Asystole, severe hypotension, and heart failure
Proton-pump inhibitors	Antifungals itraconazole ketoconazole	Proton-pump inhibitors reduce absorption of itraconazole and ketoconazole

Proton-pump inhibitors	Raltegravir	Proton-pump inhibitors possibly increase plasma concentration of raltegravir (avoid concomitant use)
Proton-pump inhibitors	Digoxin	Possibly slightly increase plasma concentration of digoxin
Pyridoxine	Levodopa	Antagonism of effects of levodopa unless carbidopa also given
Pyrimethamine	Methotrexate*	Antifolate effect of methotrexate increased
Pyrimethamine	Phenytoin*	Antagonism of anticonvulsant effect; increased antifolate effect
Pyrimethamine	Silver sulfadiazine*	Increased antifolate effect
Pyrimethamine	Sulfadiazine*	Increased antifolate effect
Pyrimethamine	Sulfamethoxazole* + trimethoprim	Increased antifolate effect
Pyrimethamine	Trimethoprim*	Increased antifolate effect
Pyrimethamine	Zidovudine	Increased antifolate effect
Pyrimethamine + sulfadoxine		See pyrimethamine
Quinine	Chloroquine	Increased risk of ventricular arrhythmias
Quinine	Digoxin*	Plasma concentration of digoxin increased
Quinolones	Analgesics	Possible increased risk of convulsions when quinolones given with NSAIDs; manufacturer of ciprofloxacin advises avoid premedication with opioid analgesics (reduced plasma concentration of ciprofloxacin) when ciprofloxacin used for surgical prophylaxis
Quinolones	Antacids	Absorption of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin reduced by antacids
Quinolones	Anti-arrhythmics	Increased risk of ventricular

		arrhythmias when levofloxacin or moxifloxacin given with amiodarone (avoid concomitant use); increased risk of ventricular arrhythmias when moxifloxacin given with disopyramide (avoid concomitant use)
Quinolones	Antibiotics	Increased risk of ventricular arrhythmias when moxifloxacin given with parenteral erythromycin (avoid concomitant use); effects of nalidixic acid possibly antagonised by nitrofurantoin
Quinolones	Anticoagulants	Ciprofloxacin, nalidixic acid, norfloxacin, and ofloxacin enhance anticoagulant effect of coumarins.
Quinolones	Coumarins	Levofloxacin possibly enhances anticoagulant effect of coumarins.
Quinolones	Antidepressants	Ciprofloxacin inhibits metabolism of duloxetine (avoid concomitant use); manufacturer of agomelatine advised; increased risk of ventricular arrhythmias when moxifloxacin given with tricyclics (avoid concomitant use)
Quinolones	Antidiabetics	Norfloxacin possibly enhances effects of glibenclamide.
Quinolones	Anti-epileptics	Ciprofloxacin increases or decreases plasma concentration of phenytoin.
Quinolones	Antihistaminics	Increased risk of ventricular arrhythmias when moxifloxacin given with mizolastine (avoid concomitant use)
Quinolones	Antimalarials	Increased risk of ventricular arrhythmias when moxifloxacin given with chloroquine and

		hydroxychloroquine or quinine (avoid concomitant use)
Quinolones	Antipsychotics	Increased risk of ventricular arrhythmias when moxifloxacin given with benperidol manufacturer of benperidol advises (avoid concomitant use); increased risk of ventricular arrhythmias when moxifloxacin given with haloperidol, phenothiazines, or (avoid concomitant use); ciprofloxacin increases plasma concentration of clozapine; ciprofloxacin possibly increases plasma concentration of olanzapine
Quinolones	Sotalol	Increased risk of ventricular arrhythmias when moxifloxacin given with sotalol (avoid concomitant use)
Quinolones	Calcium salts	Absorption of ciprofloxacin reduced by calcium salts
Quinolones	Ciclosporin	Increased risk of nephrotoxicity when quinolones given with ciclosporin
Quinolones	Clopidogrel	Ciprofloxacin possibly reduces antiplatelet effect of clopidogrel.
Quinolones	Cytotoxics	Nalidixic acid increases risk of melphalan toxicity; ciprofloxacin possibly reduces excretion of methotrexate (increased risk of toxicity); ciprofloxacin increases plasma concentration of erlotinib; increased risk of ventricular arrhythmias when levofloxacin.
Quinolones	Dairy products	Absorption of ciprofloxacin and norfloxacin reduced by dairy products

Quinolones	Iron	Absorption of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin reduced by oral iron
Quinolones	Muscle relaxants	Norfloxacin possibly increases plasma concentration of tizanidine (increased risk of toxicity); avoid concomitant use.
Quinolones	Probenecid	Excretion of ciprofloxacin, nalidixic acid, and norfloxacin reduced by probenecid (increased plasma concentration)
Quinolones	Theophylline	Possible increased risk of convulsions when quinolones given with theophylline
Quinolones	Theophylline	Ciprofloxacin and norfloxacin increase plasma concentration of theophylline.
Quinolones	Gastric ulcer drugs	Absorption of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin reduced by sucralfate
Quinolones	Vaccines	Antibiotics inactivate oral typhoid vaccine.
Quinolones	Zinc	Absorption of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin reduced by zinc.
Raltegravir	Proton-pump inhibitors	Plasma concentration of raltegravir increased (avoid concomitant use)
Raltegravir	Omeprazole	Plasma concentration of raltegravir increased by omeprazole (avoid concomitant use)
Raltegravir	Antibiotics	Plasma concentration of raltegravir reduced by rifampicin (consider increasing dose of raltegravir)
Rifampicin	Abacavir	Plasma concentration of abacavir

		possibly reduced
Rifampicin	Amitriptyline	Plasma concentration of amitriptyline possibly reduced
Rifampicin	Antacids (aluminium hydroxide; magnesium hydroxide)	Reduced absorption of rifampicin
Rifampicin	Azathioprine	Manufacturers report of its interactions (may cause rejection of organ transplantation).
Rifampicin	Chloramphenicol	Accelerated metabolism of chloramphenicol (reduced plasma chloramphenicol concentration)
Rifampicin	Ciclosporin*	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
Rifampicin	Clomipramine	Plasma concentration of clomipramine possibly reduced
Rifampicin	Contraceptives, oral*	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
Rifampicin	Clonazepam	Accelerated metabolism of clonazepam (reduced plasma concentration of clonazepam)
Rifampicin	Dapsone	Reduced plasma dapsone concentration
Rifampicin	Dexamethasone*	Accelerated metabolism of dexamethasone (reduced effect)
Rifampicin	Diazepam	Metabolism of diazepam accelerated (reduced plasma concentration)
Rifampicin	Digoxin	Plasma concentration of digoxin possibly reduced
Rifampicin	Doxycycline	Plasma doxycycline concentration possibly reduced
Rifampicin	Efavirenz	Reduced plasma concentration of efavirenz (increase efavirenz dose)
Rifampicin	Fluconazole*	Accelerated metabolism of

		fluconazole (reduced plasma concentration)
Rifampicin	Glibenclamide*	Possibly accelerated metabolism (reduced effect) of glibenclamide
Rifampicin	Haloperidol*	Accelerated metabolism of haloperidol (reduced plasma haloperidol concentration)
Rifampicin	Hydrocortisone*	Accelerated metabolism of hydrocortisone (reduced effect)
Rifampicin	Indinavir*	Metabolism accelerated by rifampicin (plasma indinavir concentration reduced—avoid concomitant use)
Rifampicin	Levonorgestrel*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Rifampicin	Levothyroxine	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
Rifampicin	Lopinavir*	Reduced plasma concentration of lopinavir (avoid concomitant use)
Rifampicin	Medroxyprogesterone*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
Rifampicin	Methadone	Accelerated metabolism of methadone (reduced effect)
Rifampicin	Nelfinavir*	Plasma concentration of nelfinavir significantly reduced (avoid concomitant use)
Rifampicin	Nevirapine*	Reduced plasma concentration of nevirapine (avoid concomitant use)
Rifampicin	Nifedipine*	Accelerated metabolism of nifedipine (plasma concentration significantly reduced)

Rifampicin	Norethisterone*	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Rifampicin	Phenytoin*	Accelerated metabolism of phenytoin (reduced plasmaconcentration)
Rifampicin	Prednisolone*	Accelerated metabolism of prednisolone (reduced effect)
Rifampicin	Propranolol	Metabolism of propranolol accelerated (significantly reduced plasma concentration)
Rifampicin	Quinidine*	Accelerated metabolism of quinidine (reduced plasma quinidine concentration)
Rifampicin	Saquinavir*	Plasma concentration of saquinavir significantly reduced—avoid concomitant use
Rifampicin	Theophylline	Accelerated metabolism of theophylline (plasma concentration significantly reduced)
Rifampicin	Verapamil*	Accelerated metabolism of verapamil (plasma concentration significantly reduced)
Rifampicin	Warfarin*	Accelerated metabolism of warfarin (reduced anticoagulant effect)
Ritonavir	Amitriptyline*	Plasma concentration possibly increased by ritonavir
Ritonavir	Amlodipine*	Possibly increased plasma concentration of amlodipine
Ritonavir	Azathioprine	Plasma concentration of azithromycin possibly increased
Ritonavir	Carbamazepine*	Plasma concentration possibly increased by ritonavir
Ritonavir	ChlorpromazineI*	Plasma concentration possibly increased by ritonavir
Ritonavir	Ciclosporin*	Plasma concentration possibly increased by ritonavir

Ritonavir	Clomipramine*	Plasma concentration possibly increased by ritonavir
Ritonavir	Codeine*	Ritonavir possibly increases plasma concentration of codeine
Ritonavir	Contraceptives, oral*	Accelerated metabolism of estrogens (reduced contraceptive effect)
Ritonavir	Dexamethasone	Plasma concentration possibly increased by ritonavir
Ritonavir	Diazepam*	Plasma concentration possibly increased by ritonavir (risk of extreme sedation and respiratory depression—avoid concomitant use)
Ritonavir	Efavirenz	Increased risk of toxicity (monitor liver function tests)
Ritonavir	Erythromycine	Plasma concentration possibly increased by ritonavir
Ritonavir	Fluconazole	Plasma concentration of fluconazole increased by ritonavir
Ritonavir	Fluoxetine*	Plasma concentration possibly increased by ritonavir
Ritonavir	Fluphenazine*	Plasma concentration possibly increased by ritonavir
Ritonavir	Haloperidol*	Plasma concentration possibly increased by ritonavir
Ritonavir	Hydrocortisone	Plasma concentration possibly increased by ritonavir
Ritonavir	Ibuprofen	Plasma concentration possibly increased by ritonavir
Ritonavir	Indinavir	Ritonavir increases plasma concentration of indinavir
Ritonavir	Levonorgestrel*	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
Ritonavir	Medroxyprogesterone*	Accelerated metabolism of medroxyprogesterone (does not apply to injectable)

		medroxyprogesterone acetate used for contraception)
Ritonavir	Methadone	Reduced plasma concentration of methadone
Ritonavir	Morphine*	Ritonavir possibly increases plasma concentration of morphine
Ritonavir	Nelfinavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
Ritonavir	Nifedipine*	Plasma concentration possibly increased by ritonavir
Ritonavir	Norethisterone*	Accelerated metabolism of norethisterone (reduced contraceptive effect)
Ritonavir	Prednisolone	Plasma concentration possibly increased by ritonavir
Ritonavir	Quinidine*	Increased plasma quinidine concentration (increased risk of ventricular arrhythmias—avoid concomitant use)
Ritonavir	Saquinavir	Ritonavir increases plasma concentration of saquinavir
Ritonavir	Simvastatin*	Increased risk of myopathy
Ritonavir	Verapamil*	Plasma concentration possibly increased by ritonavir
Ritonavir	Warfarin*	Plasma concentration possibly increased by ritonavir
Salbutamol	Acetazolamide	Increased risk of hypokalaemia with high doses of salbutamol
Salbutamol	Dexamethasone	Increased risk of hypokalemia if high doses of salbutamol given with dexamethasone
Salbutamol	Digoxin	Possibly reduced plasma concentration of digoxin
Salbutamol	Furosemide	Increased risk of hypokalemia with high doses of salbutamol
Salbutamol	Hydrochlorothiazide	Increased risk of hypokalemia with

		high doses of salbutamol
Salbutamol	Hydrocortisone	Increased risk of hypokalemia if high doses of salbutamol given with hydrocortisone
Salbutamol	Methyldopa*	Acute hypotension reported with salbutamol infusion
Salbutamol	Prednisolone	Increased risk of hypokalemia if high doses of salbutamol given with prednisolone
Salbutamol	Theophylline	Increased risk of hypokalemia if high doses of salbutamol given with theophylline
Saquinavir	Carbamazepine	Possibly reduced plasma saquinavir concentration
Saquinavir	Ciclosporin*	Plasma concentration of both ciclosporin and saquinavir increased
Saquinavir	Dexamethasone	Possibly reduced plasma saquinavir concentration
Saquinavir	Efavirenz	Efavirenz significantly reduces plasma concentration of saquinavir
Saquinavir	Fluconazole	Plasma concentration of saquinavir possibly increased
Saquinavir	Indinavir	Indinavir increases plasma concentration of saquinavir
Saquinavir	Lopinavir	Increased plasma concentration of saquinavir
Saquinavir	Nelfinavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
Saquinavir	Nevirapine	Plasma concentration of saquinavir reduced
Saquinavir	Phenobarbital*	Plasma concentration of saquinavir possibly reduced
Saquinavir	Phenytoin	Plasma saquinavir concentration possibly reduced
Saquinavir	Rifampicin*	Plasma concentration of saquinavir significantly reduced—avoid

		concomitant use
Saquinavir	Ritonavir*	Ritonavir increases plasma concentration of saquinavir
Saquinavir	Simvastatin*	Increased risk of myopathy
Saquinavir	Warfarin	Possibly enhanced anticoagulant effect
Silver sulfadiazine	Note: Interactions may apply when silver sulfadiazine is used to treat large areas of skin.	
Silver sulfadiazine	Ciclosporin*	Increased risk of nephrotoxicity; possibly reduced plasma concentration of ciclosporin
Silver sulfadiazine	Glibenclamide	Effects of glibenclamide rarely enhanced
Silver sulfadiazine	Methotrexate	Increased risk of methotrexate toxicity
Silver sulfadiazine	Phenytoin	Possibly increased plasma concentration of phenytoin
Silver sulfadiazine	Pyrimethamine*	Increased antifolate effect
Silver sulfadiazine	Thiopental	Enhanced effects of thiopental
Silver sulfadiazine	Warfarin*	Enhanced anticoagulant effect
Sodium lactate, compound solution		See potassium salts and sodium hydrogen carbonate
Soluble insulins		See Insulins
Sodium stibogluconate	Antifungals	If sodium stibogluconate is administered before amphotericin B, it may increase risk of arrhythmia; manufacturers advise that there should be a 14-day gap between administration of these two drugs.
Spironolactone	Acetylsalicylic acid	Antagonism of diuretic effect
Spironolactone	Alcohol	Enhanced hypotensive effect
Spironolactone	Amitriptyline	Increased risk of postural hypotension
Spironolactone	Amlodipine	Enhanced hypotensive effect
Spironolactone	Atenolol	Enhanced hypotensive effect

Spironolactone	Carbamazepin	Increased risk of hyponatremia
Spironolactone	Chlorpromazine	Enhanced hypotensive effect
Spironolactone	Ciclosporin*	Increased risk of hyperkalemia
Spironolactone	Clomipramine	Increased risk of postural hypotension
Spironolactone	Clonazepam	Enhanced hypotensive effect
Spironolactone	Contraceptives, oral	Antagonism of diuretic effect by estrogens
Spironolactone	Dexamethasone	Antagonism of diuretic effect
Spironolactone	Diazepam	Enhanced hypotensive effect
Spironolactone	Digoxin*	Plasma concentration of digoxin increased
Spironolactone	Enalapril*	Enhanced hypotensive effect; increased risk of severe hyperkalemia (monitor plasma potassium concentration with low-dose spironolactone in heart failure)
Spironolactone	Ether, anesthetic	Enhanced hypotensive effect
Spironolactone	Fluphenazine	Enhanced hypotensive effect
Spironolactone	Glyceryl trinitrate	Enhanced hypotensive effect
Spironolactone	Halothane	Enhanced hypotensive effect
Spironolactone	Hydralazine	Enhanced hypotensive effect
Spironolactone	Hydrocortisone	Enhanced hypotensive effect
Spironolactone	Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalemia
Spironolactone	Isosorbide dinitrate	Enhanced hypotensive effect
Spironolactone	Ketamine	Enhanced hypotensive effect
Spironolactone	Levodopa	Enhanced hypotensive effect
Spironolactone	Methyldopa	Enhanced hypotensive effect
Spironolactone	Nifedipine	Enhanced hypotensive effect
Spironolactone	Nitrous oxide	Enhanced hypotensive effect
Spironolactone	Potassium salts*	Risk of hyperkalemia
Spironolactone	Prednisolone	Antagonism of diuretic effect
Spironolactone	Propranolol	Antagonism of diuretic effect

Spironolactone	Sodium nitroprusside	Antagonism of diuretic effect
Spironolactone	Thiopental	Antagonism of diuretic effect
Spironolactone	Timolol	Antagonism of diuretic effect
Spironolactone	Verapamil	Antagonism of diuretic effect
Stavudine	Doxorubicin	Doxorubicin may inhibit effects of stavudine
Stavudine	Ribavirin*	Possibly inhibited effects of stavudine
Stavudine	Zidovudine*	May inhibit effect of stavudine (avoid concomitant use)
Streptomycin	Amphotericin B	Increased risk of nephrotoxicity
Streptomycin	Capreomycin	Increased risk of nephrotoxicity and ototoxicity
Streptomycin	Ciclosporin*	Increased risk of nephrotoxicity
Streptomycin	Furosemide*	Increased risk of ototoxicity
Streptomycin	Neostigmine*	Antagonism of effect of neostigmine
Streptomycin	Pyridostigmine*	Antagonism of effect of pyridostigmine
Streptomycin	Suxamethonium*	Enhanced muscle relaxant effect
Streptomycin	Vancomycin	Increased risk of nephrotoxicity and ototoxicity
Streptomycin	Vecuronium*	Enhanced muscle relaxant effect
Sulfamethoxazole/trimethoprim	Azathioprine*	Increased risk of hematological toxicity
Sulfamethoxazole/trimethoprim	Ciclosporin*	Increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim
Sulfamethoxazole/trimethoprim	Dapsone	Plasma concentration of both dapsone and trimethoprim may increase with concomitant use.
Sulfamethoxazole/trimethoprim	Digoxin	Plasma concentration of digoxin possibly increased
Sulfamethoxazole/trimethoprim	Glibenclamide	Effect of glibenclamide rarely enhanced
Sulfamethoxazole/trimethoprim	Lamivudine	Plasma concentration of lamivudine

		increased (avoid concomitant use of high-dose sulfamethoxazole + trimethoprim)
Sulfamethoxazole/trimethoprim	Mercaptopurine*	Increased risk of hematological toxicity
Sulfamethoxazole/trimethoprim	Methotrexate*	Antifolate effect of methotrexate increased (avoid concomitant use); risk of methotrexate toxicity increased
Sulfamethoxazole/trimethoprim	Phenytoin*	Antifolate effect and plasma phenytoin concentration increased
Sulfamethoxazole/trimethoprim	Procainamide	Increased plasma procainamide concentration
Sulfamethoxazole/trimethoprim	Pyrimethamine*	Increased antifolate effect
Sulfamethoxazole/trimethoprim	Sulfadoxine* + pyrimethamine	Increased antifolate effect
Sulfamethoxazole/trimethoprim	Thiopental	Enhanced effects of thiopental
Sulfamethoxazole/trimethoprim	Warfarin*	Enhanced anticoagulant effect
Sulfasalazine	Azathioprine	Possibly increased risk of leukopenia
Sulfasalazine	Digoxin	Absorption of digoxin possibly reduced
Sulfasalazine	Folic acid and folinic acid	Absorption of digoxin possibly reduced folic acid and folinic possibly reduced absorption of folic acid
Sulfasalazine	Mercaptopurine	Possibly increased risk of leukopenia
Suxamethonium	Amikacin*	Enhanced effects of suxamethonium
Suxamethonium	Clindamycin*	Enhanced effects of suxamethonium
Suxamethonium	Cyclophosphamide	Enhanced effects of suxamethonium
Suxamethonium	Digoxin	Risk of ventricular arrhythmias
Suxamethonium	Gentamicin*	Enhanced muscle relaxant effect
Suxamethonium	Halothane	Enhanced effects of suxamethonium
Suxamethonium	Lidocaine	Neuromuscular blockade enhanced and prolonged (interaction less likely)

		when lidocaine used topically)
Suxamethonium	Magnesium (parenteral)	Enhanced muscle relaxant effect
Suxamethonium	Metoclopramide	Enhanced effects of suxamethonium
Suxamethonium	Neostigmine	Effect of suxamethonium enhanced
Suxamethonium	Paromomycin*	Possibly enhanced effects of suxamethonium
Suxamethonium	Procainamide*	Enhanced muscle relaxant effect
Suxamethonium	Propranolol	Enhanced muscle relaxant effect
Suxamethonium	Pyridostigmine	Effect of suxamethonium enhanced
Suxamethonium	Quinidine*	Enhanced muscle relaxant effect
Suxamethonium	Quinine	Possibly enhanced effects of suxamethonium
Suxamethonium	Streptomycin*	Enhanced muscle relaxant effect
Suxamethonium	Vancomycin *	Enhanced effects of suxamethonium
Suxamethonium	Verapamil	Enhanced effects of suxamethonium
Tenofovir	Lopinavir	Plasma concentration of tenofovir increased
Thiopental	Acetazolamide	Enhanced hypotensive effect
Thiopental	Amiloride	Enhanced hypotensive effect
Thiopental	Amlodipine	Enhanced hypotensive effect
Thiopental	Amitriptyline	Increased risk of arrhythmias and hypotension
Thiopental	Chlorpromazine*	Enhanced hypotensive effect
Thiopental	Clomipramine	Increased risk of arrhythmias and hypotension
Thiopental	Diazepam	Enhanced sedative effect
Thiopental	Enalapril	Enhanced hypotensive effect
Thiopental	Fluphenazine*	Enhanced hypotensive effect
Thiopental	Furosemide	Enhanced hypotensive effect
Thiopental	Glyceryl trinitrate	Enhanced hypotensive effect
Thiopental	Haloperidol*	Enhanced hypotensive effect
Thiopental	Hydralazine	Enhanced hypotensive effect
Thiopental	Hydrochlorothiazide	Enhanced hypotensive effect
Thiopental	Isoniazid	Possible potentiation of isoniazid hepatotoxicity
Thiopental	Isosorbide dinitrate	Enhanced hypotensive effect

Thiopental	Methyldopa	Enhanced hypotensive effect
Thiopental	Nifedipine	Enhanced hypotensive effect
Thiopental	Propranolol	Enhanced hypotensive effect
Thiopental	Silver sulfadiazine	Enhanced effects of thiopental
Thiopental	Sodium nitroprusside	Enhanced hypotensive effect
Thiopental	Spironolactone	Enhanced hypotensive effect
Thiopental	Sulfadiazine	Enhanced effects of thiopental
Thiopental	Sulfadoxine + pyrimethamine	Enhanced effects of thiopental
Thiopental	Sulfamethoxazole + trimethoprim	Enhanced effects of thiopental
Thiopental	Timolol	Enhanced hypotensive effect
Thiopental	Vancomycin	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
Thiopental	Verapamil*	Enhanced hypotensive effect and AV delay
Timolol		Note: Systemic absorption may follow topical application of timolol to the eye
Timolol	Acetazolamide	Enhanced hypotensive effect
Timolol	Alcohol	Enhanced hypotensive effect
Timolol	Amiloride	Enhanced hypotensive effect
Timolol	Amlodipine	Enhanced hypotensive effect
Timolol	Chlorpromazine	Enhanced hypotensive effect
Timolol	Diazepam	Enhanced hypotensive effect
Timolol	Digoxin	Increased AV block and bradycardia
Timolol	Enalapril	Enhanced hypotensive effect
Timolol	Epinephrine*	Severe hypertension
Timolol	Fluphenazine	Enhanced hypotensive effect

Timolol	Furosemide	Enhanced hypotensive effect
Timolol	Glyceryl trinitrate	Enhanced hypotensive effect
Timolol	Halothane	Enhanced hypotensive effect
Timolol	Hydralazine	Enhanced hypotensive effect
Timolol	Hydrochlorothiazide	Enhanced hypotensive effect
Timolol	Insulins	Enhanced hypoglycaemic effect; timolol may mask warning signs of hypoglycaemia such as tremor
Timolol	Isosorbide dinitrate	Enhanced hypotensive effect
Timolol	Ketamine	Enhanced hypotensive effect
Timolol	Levodopa	Enhanced hypotensive effect
Timolol	Lidocaine*	Increased myocardial depression (interaction less likely when lidocaine used topically)
Timolol	Metformin	Timolol may mask warning signs of hypoglycemia such as tremor
Timolol	Methyldopa	Enhanced hypotensive effect
Timolol	Nifedipine*	Enhanced hypotensive effect; possibly severe hypotension and heart failure
Timolol	Nitrous oxide	Enhanced hypotensive effect
Timolol	Pilocarpine	Increased risk of arrhythmias
Timolol	Procainamide*	Increased myocardial depression
Timolol	Quinidine*	Increased myocardial depression
Timolol	Sodium nitroprusside	Enhanced hypotensive effect
Timolol	Spironolactone	Enhanced hypotensive effect
Timolol	Thiopental	Enhanced hypotensive effect
Timolol	Verapamil*	Asystole, severe hypotension, and heart failure
Tramadol	Analgesics: See Opioid analgesic	
Vaccine, live	Note: Vaccine, live, includes BCG, cholera (oral), measles, MMR, poliomyelitis (oral), rubella, typhoid, varicella, and yellow fever vaccines.	
Vaccine, live	Azathioprine*	Avoid use of live vaccines with

		azathioprine (impairment of immune response).
Vaccine, live	Bleomycin	Avoid use of live vaccines with bleomycin (impairment of immune response).
Vaccine, live	Chlorambucil	Avoid use of live vaccines with chlorambucil (impairment of immune response).
Vaccine, live	Ciclosporin*	Avoid use of live vaccines with ciclosporin (impairment of immune response).
Vaccine, live	Cisplatin	Avoid use of live vaccines with cisplatin (impairment of immune response).
Vaccine, live	Cyclophosphamide	Avoid use of live vaccines with cyclophosphamide (impairment of immune response).
Vaccine, live	Cytarabine	Avoid use of live vaccines with cytarabine (impairment of immune response).
Vaccine, live	Dacarbazine	Avoid use of live vaccines with dacarbazine (impairment of immune response).
Vaccine, live	Dactinomycin	Avoid use of live vaccines with dactinomycin (impairment of immune response).
Vaccine, live	Daunorubicin	Avoid use of live vaccines with daunorubicin (impairment of immune response).
Vaccine, live	Dexamethasone*	High doses of dexamethasone impair immune response; avoid use of live vaccines with dexamethasone.
Vaccine, live	Doxorubicin	Avoid use of live vaccines with doxorubicin (impairment of immune response)
Vaccine, live	Fluorouracil	Avoid use of live vaccines with

		fluorouracil (impairment of immune response).
Vaccine, live	Hydrocortisone*	High doses of hydrocortisone impair immune response; avoid use of live vaccines with hydrocortisone.
Vaccine, live	Immunoglobulin (human), anti-D*	Avoid use of live virus vaccines during <i>4 weeks before</i> or during <i>3 months after</i> injection of anti-D immunoglobulin (impairment of immune response) but rubella vaccine (either as MMR or single-antigen rubella vaccine) may be given at the same time as anti-D immunoglobulin.
Vaccine, live	Immunoglobulin, human normal	Avoid use of live vaccines during <i>3 weeks before</i> or during <i>3 months after</i> injection of human normal immunoglobulin (impairment of immune response).
Vaccine, Live	Mercaptopurine	Avoid use of live vaccines with mercaptopurine (impairment of immune response).
Vaccine, live	Methotrexate	Avoid use of live vaccines with methotrexate (impairment of immune response).
Vaccine, live	Prednisolone*	High doses of prednisolone impair immune response; avoid use of live vaccines with prednisolone.
Vaccine, live	Procarbazine	Avoid use of live vaccines with procarbazine (impairment of immune response).
Vaccine, live	Vinblastine	Avoid use of live vaccines with vinblastine (impairment of immune response).
Vaccine, live	Vincristine	Avoid use of live vaccines with vincristine (impairment of immune response).

Valproic acid	Acetylsalicylic acid	Enhancement of effect of valproic acid
Valproic acid	Amitriptyline*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Valproic acid	Carbamazepine	Possible enhanced toxicity without corresponding increase in anti-epileptic effect; plasma concentration of valproic acid reduced; plasma concentration of active metabolite of carbamazepine increased
Valproic acid	Chloroquine*	Possibly increased risk of convulsions
Valproic acid	Chlorpromazine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Valproic acid	Clomipramin*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Valproic acid	Erythromycin	Metabolism of valproic acid possibly inhibited (increased plasma concentration)
Valproic acid	Ethosuximide	Possible enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of ethosuximide possibly increased
Valproic acid	Fluphenazine*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Valproic acid	Haloperidol*	Antagonism of anticonvulsant effect (convulsive threshold lowered)
Valproic acid	Phenobarbital	Possible enhanced toxicity without corresponding increase in anti-epileptic effect; plasma concentration of valproic acid reduced; phenobarbital concentration increased
Valproic acid	Phenytoin	Possible enhanced toxicity without corresponding increase in anti-

		epileptic effect; plasma concentration of valproic acid reduced; plasma concentration of phenytoin increased or possibly reduced
Valproic acid	Warfarin	Anticoagulant effect possibly enhanced
Valproic acid	Zidovudine	Plasma concentration of zidovudine possibly increased (risk of toxicity)
Verapamil	Acetazolamide	Enhanced hypotensive effect
Verapamil	Alcohol	Enhanced hypotensive effect; plasma concentration of alcohol possibly increased by verapamil
Verapamil	Amiloride	Enhanced hypotensive effect
Verapamil	Amitriptyline	Possibly increased plasma concentration of amitriptyline
Verapamil	Atenolol*	Asystole, severe hypotension, and heart failure
Verapamil *	Carbamazepine*	Enhanced effect of carbamazepine
Verapamil	Chlorpromazine	Enhanced hypotensive effect
Verapamil	Ciclosporin*	Increased plasma ciclosporin concentration
Verapamil	Anti-arrhythmic drugs, e.g., amiodarone	If both drugs used concomitantly may increase risk of bradycardia, AV block and myocardial depression.
Verapamil	Clarithromycin and erythromycin	Metabolism of erythromycin and clarithromycin may be inhibited (increased risk of toxicity)
Verapamil	Clomipramine	Possibly increased plasma concentration of clomipramine
Verapamil	Clonazepam	Enhanced hypotensive effect
Verapamil	Contraceptives, oral	Antagonism of hypotensive effect by estrogens
Verapamil	Dexamethasone	Antagonism of hypotensive effect
Verapamil	Diazepam, and other sedatives	Enhanced hypotensive effect

Verapamil	Digoxin*	Increased plasma concentration of digoxin; increased AV block and bradycardia
Verapamil	Enalapril	Enhanced hypotensive effect
Verapamil	Erythromycine*	Possible inhibition of metabolism of verapamil (increased risk of toxicity)
Verapamil	Ether, anesthetic	Enhanced hypotensive effect
Verapamil	Fluphenazine	Enhanced hypotensive effect
Verapamil	Furosemide	Enhanced hypotensive effect
Verapamil	Glyceryl trinitrate	Enhanced hypotensive effect
Verapamil	Grapefruit juice	Increased plasma verapamil concentration
Verapamil	Haloperidol	Enhanced hypotensive effect
Verapamil	Halothane*	Enhanced hypotensive effect and AV delay
Verapamil	Hydralazine	Enhanced hypotensive effect
Verapamil	Hydrochlorothiazide	Enhanced hypotensive effect
Verapamil	Hydrocortisone	Antagonism of hypotensive effect
Verapamil	Ibuprofen	Antagonism of hypotensive effect
Verapamil	Isosorbide dinitrate	Enhanced hypotensive effect
Verapamil	Ketamine*	Enhanced hypotensive effect and AV delay
Verapamil	Levodopa	Enhanced hypotensive effect
Verapamil	Lidocaine*	Increased risk of myocardial depression (interaction less likely when lidocaine used topically)
Verapamil	Methyldopa	Enhanced hypotensive effect
Verapamil	Nitrous oxide*	Enhanced hypotensive effect and AV delay
Verapamil	Phenobarbital*	Effect of verapamil probably reduced
Verapamil	Phenytoin	Reduced effect of verapamil
Verapamil	Prednisolone	Antagonism of hypotensive effect
Verapamil	Propranolol*	Asystole, severe hypotension, and heart failure
Verapamil	Quinidine*	Increased plasma quinidine

		concentration (extreme hypotension may occur)
Verapamil	Rifampicin*	Accelerated metabolism of verapamil (plasma concentration significantly reduced)
Verapamil	Ritonavir*	Plasma concentration possibly increased by ritonavir
Verapamil	Simvastatin*	Increased risk of myopathy
Verapamil	Sodium nitroprusside	Enhanced hypotensive effect
Verapamil	Spironolactone	Enhanced hypotensive effect
Verapamil	Suxomethonium	Enhanced effects of suxamethonium
Verapamil	Theophylline	Increased effect of theophylline (increased plasma concentration of theophylline)
Verapamil	Thiopental*	Enhanced hypotensive effect and AV delay
Verapamil	Timolol*	Asystole, severe hypotension, and heart failure
Verapamil	Vecuronium	Enhanced muscle relaxant effect
Zidovudine		Note: Its administration with nephrotoxic drugs and myelosuppressive drugs may enhance their toxic effects.
Zidovudine	Fluconazole*	Increased plasma concentration of zidovudine (increased risk of toxicity)
Zidovudine	Ibuprofen	Increased risk of hematological toxicity
Zidovudine	Methadone	Possibly increased plasma concentration of zidovudine
Zidovudine	Phenytoin	Plasma phenytoin concentration increased or decreased by zidovudine
Zidovudine	Pyrimethamine	Increased antifolate effect
Zidovudine	Ribavirin*	Possibly inhibited effect of zidovudine

Zidovudine	Rifampicin*	Manufacturer of zidovudine advises avoid concomitant use
Zidovudine	Stavudine*	May inhibit effect of stavudine (avoid concomitant use)
Zidovudine	Valproic acid	Plasma concentration of zidovudine possibly increased (risk of toxicity)
Zinc oxide	Calcium salts	Reduced absorption of zinc
Zinc sulfate	Antibiotics	Reduced absorption of ciprofloxacin, moxifloxacin, norfloxacin, ofloxacin
Zinc sulfate	Calcium salts	Reduced absorption of zinc
Zinc sulfate	Tetracyclines	Reduced absorption of zinc
Zinc sulfate	Ferrous salts	Absorption of zinc and of oral ferrous salts reduced
Zinc sulfate	Penicilliamine	Absorption of both drugs reduced

APPENDIX B: Pregnancy

During pregnancy, the mother and the fetus form a non-separable functional unit. Maternal well-being is an absolute prerequisite for the optimal functioning and development of both parts of this unit. Consequently, it is important to treat the mother whenever needed while protecting the unborn child to the greatest possible extent.

Drugs can have harmful effects on the fetus at any time during pregnancy. It is important to remember this when prescribing for a woman of childbearing age or for a man trying to father a child. However, irrational fear of using drugs during pregnancy can also result in harm. Untreated illness, impaired maternal compliance, sub-optimal treatment, and treatment failures may all pose a risk to maternal well-being, and may also affect the unborn child. It is important to know the “background risk” in the context of the prevalence of drug-induced adverse pregnancy outcomes. Major congenital malformations occur in 2–4% of all live births. Up to 15% of all diagnosed pregnancies will result in fetal loss. The cause of these adverse pregnancy outcomes is understood in only a minority of cases.

During the *first* trimester, drugs may produce congenital malformations (teratogenesis), and the greater risk is from the third to the eleventh week of pregnancy. During the *second* and *third* trimesters, drugs may affect the growth and functional development of the fetus or have toxic effects on fetal tissues. Drugs given shortly before term or during labor may have adverse effects on labor or on the neonate after delivery. Few drugs have been shown conclusively to be teratogenic in humans, but no drug is safe beyond all doubt in early pregnancy.

Prescribing in pregnancy

If possible, counseling of women before a planned pregnancy should be carried out, including discussion of risks associated with specific therapeutic agents, traditional medicines, and abuse of substances such as nicotine and alcohol. Folic acid supplements should be given during pregnancy planning because periconceptual use of folic acid reduces neural tube defects.

Drugs should be prescribed in pregnancy only if the expected benefits to the mother are thought to be greater than the risk to the fetus. All drugs should be avoided if possible during the first trimester. Drugs that have been used extensively in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs, and the smallest effective dose should be used. Well-known single-component drugs should usually be preferred to multicomponent drugs.

The following table lists drugs that may have harmful effects in pregnancy and indicates the trimester of risk. It is based on human data but information on animal studies has been included for some drugs when its omission might be misleading.

Absence of a medicine from the list below does not imply safety.

List of medicines that may have harmful effects in pregnancy

Medicine	Comments
Abacavir	Toxicity in animal studies
Acetazolamide	Not used to treat hypertension in pregnancy. First trimester: Avoid (toxicity in animal studies).
Acetylsalicylic acid	Third trimester: Impaired platelet function and risk of haemorrhage; delayed onset and increased duration of labor with increased blood loss; avoid analgesic doses if possible in last few weeks (low doses probably not

	harmful); with high doses, closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension in the newborn; kernicterus in jaundiced neonates.
Aciclovir	Not known to be harmful; limited absorption from topical preparations
Albendazole	Contraindicated in cestode infections. First trimester: avoid in nematode infections.
Allopurinol	Toxicity not reported. Use only if no safer alternative and disease carries risk for mother or child.
Aminophylline	Neonatal irritability and apnea have been reported.
Amitriptyline	Manufacturer advises to avoid unless essential, particularly during first and third trimesters.
Amlodipine	No information on use in humans. Risk to fetus should be balanced against risk of uncontrolled maternal hypertension.
Amoxicilline	Not known to be harmful
Amoxicilline + clavulanic acid	See Amoxicillin.
Ampicillin	Not known to be harmful
Artemether	First trimester: Avoid.
Artesunate	First trimester: Avoid.
Atazanavir + ritonavir	Data not available but to use only when benefits outweigh risks.
Atenolol	May cause intrauterine growth restriction, neonatal hypoglycemia, and bradycardia; risk greater in severe hypertension
Atropine	Not known to be harmful
Azithromycin	Limited information available. Use only if adequate alternatives not available.
Beclometasone	Benefit of treatment, for example, in asthma, outweighs risk.
Benzathine benzylpenicillin	Not known to be harmful
Benzylpenicillin	Not known to be harmful
Betamethasone	Benefit of treatment, for example, in asthma,

	outweighs risk.
Bisacodyl	If dietary and lifestyle changes fail to control constipation in pregnancy, moderate doses of poorly absorbed laxatives may be used. A bulk-forming laxative should be tried first. An osmotic laxative, such as lactulose, can also be used. Bisacodyl or senna may be suitable if a stimulant effect is necessary.
Bromocriptine	Use with caution.
Bupivacaine	Third trimester: With large doses, neonatal respiratory depression, hypotonia, and bradycardia after paracervical or epidural block; lower doses of bupivacaine for intrathecal use during late pregnancy
Captopril	ACE inhibitors should be avoided in pregnancy unless essential. They may adversely affect fetal and neonatal blood pressure control and renal function; skull defects and oligohydramnios have also been reported.
Carbamazepine	First trimester: Risk of teratogenesis including increased risk of neural tube defects (counseling and screening and adequate folate supplements advised, for example, 5 mg daily); risk of teratogenicity greater if more than one antiepileptic used; see Section 5. 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.
Carbimazole	Neonatal goiter and hypothyroidism; has been associated with congenital defects including aplasia cutis of the neonate; the use of carbimazole in pregnancy is recommended only if propylthiouracil is not suitable.
Ceftriaxone	Not known to be harmful
Chloramphenicol	Third trimester: Neonatal "gray" syndrome
Chloroquine	First and third trimesters: Benefit of prophylaxis

	and treatment in malaria outweighs risk; important: see Section 6.5.3.
Chlorphenamine	No evidence of teratogenicity
Chlorpromazine	Third trimester: Extrapyramidal effects have been reported occasionally in the neonate when antipsychotic drugs are taken during the third trimester of pregnancy.
Ciprofloxacin	Avoid (arthropathy in animal studies); safer alternatives are available.
Clindamycin	Not known to be harmful
Clomifene	Possible effects on fetal development
Clomipramine	Manufacturer advises to avoid unless essential, particularly during first and third trimesters.
Cloxacillin	Not known to be harmful
Contraceptives, oral	Epidemiological evidence suggests no harmful effects on fetus.
Dapsone	Third trimester: Neonatal hemolysis and methemoglobinaemia; folic acid, 5 mg daily, should be given to mother.
Deferoxamine	Teratogenic in animal studies. Manufacturer advises use only if potential benefit outweighs risk.
Diazepam	Avoid regular use (risk of neonatal withdrawal symptoms); use only if clear indication such as seizure control (high doses during late pregnancy or labor may cause neonatal hypothermia, hypotonia, and respiratory depression).
Diclofenac	Most manufacturers advise avoiding use of NSAIDs during pregnancy or avoiding them unless the potential benefit outweighs the risk. NSAIDs should be avoided during the third trimester because use is associated with a risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn. In addition, the onset of labor may be delayed and its duration

	may be increased.
Digoxin	May need dosage adjustment
Doxycycline	First trimester: Effects on skeletal development in animal studies. Second and third trimesters: Dental discoloration; maternal hepatotoxicity with large doses
Efavirenz	Avoid (potential teratogenic effects).
Emtricitabine	No information available; use only if essential.
Enalapril	Avoid; may adversely affect fetal and neonatal blood pressure control and renal function; also possible skull defects and oligohydramnios; toxicity in animal studies.
Enfuvirtide	Manufacturer advises use only if potential benefit outweighs risk.
Enoxaparin	Not known to be harmful
Ergocalciferol	High doses teratogenic in animals but therapeutic doses unlikely to be harmful
Ergotamine	Avoid; oxytocic effect on the uterus.
Erythromycin	Not known to be harmful
Ethambutol	Not known to be harmful
Ethinylestradiol	Epidemiological evidence suggests no harmful effects on fetus.
Ethosuximide	First trimester: May possibly be teratogenic; risk of teratogenicity greater if more than one anti-epileptic used
Etravirine	Manufacturer advises use only if potential benefit outweighs risk.
Fansidar	Risk of teratogenic effects in first trimester
Fenofibrate	Manufacturers advise to avoid; embryotoxicity in animal studies.
Flumazenil	May cross placenta in small amounts. Avoid unless potential benefit outweighs risk.
Fluorouracil	Avoid (teratogenic).
Fluoxetine	Manufacturer advises use only if potential benefit outweighs risk; risk of neonatal withdrawal.

Fluphenazine	Third trimester: Extrapyramidal effects in neonate occasionally reported
Fosamprenavir + ritonavir	Recommended only if the benefits of the medicine outweigh the harms.
Furosemide	Not used to treat hypertension in pregnancy
Gentamicin	Second and third trimesters: Auditory or vestibular nerve damage; risk probably very small with gentamicin, but avoid unless essential (if given, serum gentamicin concentration monitoring essential)
Glibenclamide	Third trimester: Neonatal hypoglycemia. Insulin is normally substituted in all diabetics; if oral drugs are used, therapy should be stopped at least 2 days before delivery.
Griseofulvin	Avoid (fetotoxicity and teratogenicity in animals); use effective contraception during and for at least 1 month after administration. (Important: effectiveness of oral contraceptives reduced). Also men should avoid fathering a child during and for at least 6 months after administration.
Haloperidol	Third trimester: Extrapyramidal effects in neonate occasionally reported
Halothane	Third trimester: Depresses neonatal respiration
Heparin	Maternal osteoporosis has been reported after prolonged use; multidose vials may contain benzyl alcohol; some manufacturers advise to avoid.
Hydralazine	Avoid during first and second trimesters; no reports of serious harm following use in third trimester
Hydrochlorothiazide	Not used to treat hypertension in pregnancy. Third trimester: May cause neonatal thrombocytopenia
Hydrocortisone	Benefit of treatment, for example in asthma, outweighs risk; risk of intrauterine growth retardation on prolonged or repeated systemic

	treatment; corticosteroid cover required by mother during labor; monitor closely if fluid retention.
Hyoscine	Manufacturer advises use only if potential benefit outweighs risk; injection of hyoscine may cause neonatal respiratory depression.
Ibuprofen	Avoid unless potential benefit outweighs risk. Third trimester: With regular use, closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension in the newborn; delayed onset and increased duration of labor.
Imipramine	Colic, tachycardia, dyspnea, irritability, and muscle spasms reported in neonates when used in the third trimester
Indinavir	Avoid if possible in first trimester; theoretical risk of hyperbilirubinemia and renal stones in neonates if used at term
Insulin	Insulin requirements should be assessed frequently by an experienced diabetes clinician.
Iodine	Second and third trimesters: Neonatal goiter and hypothyroidism
Iron dextran	Avoid in first trimester
Isofluran	May depress neonatal respiration if used during delivery
Isoniazid	Not known to be harmful
Ketamine	Third trimester: Depresses neonatal respiration
Ketoconazole	Manufacturer advises to avoid unless potential benefit outweighs risk (teratogenicity in animal studies)
Lactulose	Not known to be harmful
Lamivudine	Avoid if possible in first trimester; benefit of treatment considered to outweigh risk in second and third trimesters
Lamivudine + zidovudine	Avoid if possible in first trimester; benefit of treatment considered to outweigh risk in second and third trimesters

Lamivudine + nevirapine + zidovudine	Avoid if possible in first trimester; benefit of treatment considered to outweigh risk in second and third trimesters
Levodopa + carbidopa	Toxicity in animal studies
Levonorgestrel	In oral contraceptives, epidemiological evidence suggests no harmful effects on fetus
Levothyroxine	Monitor maternal serum thyrotrophin concentration; levothyroxine may cross the placenta and excessive dosage can be detrimental to fetus.
Lidocaine	Third trimester: With large doses, neonatal respiratory depression, hypotonia, and bradycardia after paracervical or epidural block
Lopinavir + ritonavir	Avoid if possible in first trimester; avoid oral solution due to high propylene glycol content.
Magnesium sulfate	Third trimester: Not known to be harmful for short-term intravenous administration in eclampsia but excessive doses may cause neonatal respiratory depression
Mebendazole	Toxicity in animal studies. Contraindicated in cestode infections. First trimester: Avoid in nematode infections
Medroxyprogesterone acetate	Avoid (genital malformations and cardiac defects acetate reported in male and female fetuses); inadvertent use of depot medroxyprogesterone acetate contraceptive injection in pregnancy unlikely to harm fetus
Metformin	All trimesters: Avoid; insulin is normally substituted in all diabetics.
Methadone	Third trimester: Depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labor
Methotrexate	Avoid (teratogenic); fertility may be reduced during therapy but this may be reversible; use effective contraception during and for at least 6 months after administration to men or women;

	see Section 8.2.
Methyldopa	Not known to be harmful
Metoclopramide	Not known to be harmful
Metoprolol	Beta-blockers may cause intrauterine growth restriction, neonatal hypoglycaemia, and bradycardia; the risk is greater in severe hypertension.
Metronidazole	Avoid high-dose regimens.
Midazolam	Avoid regular use (risk of neonatal withdrawal symptoms); use only if clear indication such as seizure control (high doses during late pregnancy or labor may cause neonatal hypothermia, hypotonia, and respiratory depression).
Morphine	Third trimester: Depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labor
Mupirocin	Manufacturer advises to avoid unless potential benefit outweighs risk; no information available.
Nalidixic acid	Quinolones should be avoided in pregnancy because they have been shown to cause arthropathy in animal studies; safer alternatives are available. However, a single dose of ciprofloxacin may be used for the prevention of a secondary case of meningococcal meningitis.
Naloxone	Use only if potential benefit outweighs risk.
Nelfinavir	Avoid if possible in first trimester; potential benefit of treatment considered to outweigh risk in second and third trimesters
Neomycine	There is a risk of auditory or vestibular nerve damage when aminoglycosides are used in the second and third trimesters of pregnancy. The risk is greatest with streptomycin. The risk is probably very small with gentamicin and tobramycin, but their use should be avoided unless essential (if given, serum

	aminoglycoside concentration monitoring is essential).
Neostigmine	Third trimester: Neonatal myasthenia with large doses
Nevirapine	Avoid if possible in first trimester; benefit of treatment considered to outweigh risk in second and third trimesters
Niclosamide	<i>T. solium</i> infections in pregnancy should be treated immediately.
Nifedipine	Some dihydropyridines are teratogenic in animals, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension; may inhibit labour (used for premature labor).
Nitrofurantoin	Third trimester: May produce neonatal hemolysis if used at term
Nitrous oxide	Third trimester: Depresses neonatal respiration
Nortriptyline	Use only if potential benefit outweighs risk.
Nystatin	No information available, but absorption from gastrointestinal tract negligible
Omeprazole	Not known to be harmful
Opium tincture	To be used only if benefits outweighs risk
Paracetamol	Not known to be harmful
Penicillamine	Fetal abnormalities reported rarely; avoid if possible
Pentavalent antimony compounds	Potentially fatal visceral leishmaniasis must be treated without delay.
Pethidine	Respiratory depression and withdrawal symptoms can occur in the neonate if opioid analgesics are used during delivery; also gastric stasis and inhalation pneumonia has been reported in the mother if opioid analgesics are used during labor.
Phenobarbital	First and third trimesters: Congenital malformations— risk of teratogenicity are greater if more than one anti-epileptic used; 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.
Phenoxymethylpenicillin	Not known to be harmful
Phytomenadione	No specific information available; use only if potential benefit outweighs risk
Potassium iodide	Second and third trimesters: Neonatal goiter and hypothyroidism
Povidone iodine	Second and third trimesters: Sufficient iodine may be absorbed to affect the fetal thyroid
Prednisolone	Benefit of treatment, for example, in asthma, outweighs risk; risk of intrauterine growth retardation on prolonged or repeated systemic treatment; corticosteroid cover required by mother during labor; monitor closely if fluid retention
Primaquine	Third trimester: Neonatal hemolysis and methaemoglobinemia; delay treatment until after delivery
Promethazine	No evidence of teratogenicity
Propofol	May depress neonatal respiration if used during delivery; maximum dose for maintenance of anesthesia 6 mg/kg/hour
Propranolol	May cause intrauterine growth restriction, neonatal hypoglycemia, and bradycardia; risk greater in severe hypertension
Pyrazinamide	Use only if potential benefit outweighs risk.
Pyrimethamine	First trimester: Theoretical teratogenic risk (folate antagonist). Adequate folate supplements should be given to the mother; avoid in pneumocystosis and toxoplasmosis; see Sulfadiazine
Quinine	First trimester: High doses are teratogenic; but in malaria benefit of treatment outweighs risk.
Raltegravir	Manufacturer advises to avoid; toxicity in animal studies.
Ranitidine	Not known to be harmful

Retinol	First trimester: Excessive doses may be teratogenic.
Rifampicin	First trimester: Very high doses teratogenic in animal studies. Third trimester: Risk of neonatal bleeding may be increased.
Ritonavir	Avoid if possible in first trimester; avoid oral solution due to high propylene glycol content.
Salbutamol	Appropriate to use for asthma; high doses should be given by inhalation only—parenteral use can affect the myometrium and possibly cause cardiac problems.
Saquinavir	Avoid if possible in first trimester; potential benefit of treatment considered to outweigh risk in second and third trimesters
Silver sulfadiazine	Third trimester: Neonatal hemolysis and methemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded.
Sodium stibogluconate	Manufacturer advises use only if potential benefit outweighs risk.
Spironolactone	Toxicity in animal studies
Stavudine	Avoid if possible in first trimester; increased risk of lactic acidosis and hepatic steatosis.
Streptokinase	Possibility of premature separation of placenta in first 18 weeks; theoretical possibility of fetal hemorrhage throughout pregnancy; risk of maternal hemorrhage on postpartum use
Streptomycin	Second and third trimesters: Auditory or vestibular nerve damage; avoid unless essential (if given, serum streptomycin concentration monitoring essential).
Sulfadoxine + pyrimethamine	In malaria, benefit of prophylaxis and treatment outweigh risk. First trimester: Possible teratogenic risk (pyrimethamine is a folate antagonist). Third trimester: Neonatal hemolysis and methemoglobinemia; fear of increased risk of kernicterus in neonates

	appears to be unfounded.
Sulfamethoxazole + trimethoprim	First trimester: Teratogenic risk (trimethoprim is a folate antagonist). Third trimester: Neonatal hemolysis and methemoglobinemia; fear of increased risk of kernicterus in neonates appears to be unfounded.
Sulfasalazine	Third trimester: Theoretical risk of neonatal hemolysis; adequate folate supplements should be given to mother.
Suxamethonium	Mildly prolonged maternal paralysis may occur.
Tenofovir	No information available; use only if potential benefit outweighs risk
Terbinafine	Manufacturer advises use only if potential benefit outweighs risk; no information available.
Tetracycline	First trimester: Effects on skeletal development in animal studies. Second and third trimesters: Dental discoloration; maternal hepatotoxicity with large doses
Theophylline	Neonatal irritability and apnea have been reported.
Thiopental	Third trimester: Depresses neonatal respiration; dose should not exceed 250 mg.
Tramadol	Embryotoxic in animal studies; manufacturers advise to avoid. Respiratory depression and withdrawal symptoms can occur in the neonate if opioid analgesics are used during delivery; also gastric stasis and inhalation pneumonia has been reported in the mother if opioid analgesics are used during labor.
Trihexyphenidyl	Use only if potential benefit outweighs risk.
Trimethoprim	First trimester: Teratogenic risk (folate antagonist)
Vaccine, BCG	First trimester: Theoretical risk of congenital malformations, but need for vaccination may outweigh possible risk to fetus
Vaccine, measles	First trimester: Theoretical risk of congenital malformations, but need for vaccination may

	outweigh possible risk to fetus; avoid MMR
Vaccine, MMR	Avoid; pregnancy should be avoided for 1 month after immunization.
Vaccine, poliomyelitis, live	First trimester: Theoretical risk of congenital malformations, but need for vaccination may outweigh possible risk to fetus
Vaccine, rubella	Avoid; pregnancy should be avoided for 1 month after immunization.
Valproic acid	First and third trimesters: Increased risk of congenital malformations and developmental delay (counseling and screening advised—folic acid supplements may reduce risk of neural tube defects); risk of teratogenicity greater if more than one anti-epileptic used; neonatal bleeding (related to hypofibrinemia) and neonatal hepatotoxicity also reported
Vecuronium	No information available; use only if potential benefit outweighs risk
Verapamil	May reduce uterine blood flow with fetal hypoxia; may inhibit labor
Zidovudine	Avoid if possible in first trimester; benefit of treatment is considered to outweigh risk in second and third trimesters.

APPENDIX C: Breast-feeding

Administration of some drugs (for example, ergotamine) to nursing mothers may harm the infant, whereas administration of others (for example, digoxin) has little effect. Some drugs inhibit lactation (for example, estrogens).

Toxicity to the infant can occur if the drug enters the breast milk in pharmacologically significant quantities. The concentration in milk of some drugs (for example, iodides) may exceed the concentration in the maternal plasma so that therapeutic doses in the mother may cause toxicity to the infant. Some drugs inhibit the infant's sucking reflex (for example, phenobarbital). Drugs in breast milk may, at least theoretically, cause hypersensitivity in the infant even when the concentration is too low for a pharmacological effect.

The following table lists drugs:

- That should be used with caution or which are contraindicated in breast-feeding for any one of the reasons given above
- That, on present evidence, may be given to the mother during breast-feeding because they appear in milk in amounts that are too small to be harmful to the infant
- That are not known to be harmful to the infant although they are present in breast milk in significant amounts

For many drugs, insufficient evidence is available to provide definitive guidance and it is advisable to administer only drugs essential to a mother during breast-feeding. Because of the inadequacy of information on drugs in breast milk, the following table should be used only as a guide; **non-inclusion in the table does not imply safety.**

The Ministry of Public Health of Afghanistan follows WHO policy. Infants should be exclusively breast-fed for the first 6 months of life; thereafter, they should

receive appropriate complementary food and continue to be breast-fed up to 2 years of age or beyond.

Medicines present in breast milk

Medicine	Comment
Abacavir	If there is no safe alternative, breast-feeding is allowed during first 6 months of life.
Acarbose	Manufacturers advises to avoid.
Acetazolamide	Amount too small to be harmful
Acetylsalicylic acid	Short course safe in usual dosage; monitor infant; regular use of high doses could impair platelet function and produce hypoprothrombinemia in infant if neonatal vitamin K stores low; possible risk of Reye syndrome
Aciclovir	Significant amount in milk after systemic administration, but considered safe to use
Allopurinol	Present in milk—not known to be harmful
Aminophylline	Present in milk—irritability in infant reported
Amitriptyline	Detectable in breast milk; continue breast-feeding; adverse effects possible; monitor infant for drowsiness
Amlodipne	Presence in milk possible; monitor infant
Amoxicilline	Trace amounts in milk; safe in usual dosage; monitor infant
Amoxicilline + clavulanic acid	Trace amounts in milk
Ampicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Atazanavir + ritonavir	Breast-feeding by HIV-positive mother may transmit infection to infant; avoid.
Atenolol	Significant amounts in milk; safe in usual dosage; monitor infant
Atorvastatin	The manufacturers of atorvastatin, fluvastatin, rosuvastatin, and imvastatin advise avoiding use in mothers who are breast-feeding as there is no information available. The manufacturers of pravastatin advise against use in breast-feeding mothers as a small amount of drug is present in breast milk.
Atropine	Small amount present in milk; monitor infant
Azithromycin	Present in milk; limited information available—use only if no suitable alternative

Medicine	Comment
Beclometasone	Systemic effects in infant unlikely with maternal dose of less than equivalent of 40 mg prednisolone daily; monitor infant's adrenal function with higher doses; the amount of inhaled drug in breast milk probably too small to be harmful
Benzathine benzylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Benzylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Betamethasone	Systemic effects in infant unlikely with maternal dose of less than equivalent of 40 mg prednisolone daily; monitor infant's adrenal function with higher doses
Bromocriptine	Suppresses lactation; avoid breast-feeding if lactation prevention fails
Bupivacaine	Amount too small to be harmful
Captopril	Present in milk, manufacturers advise to avoid
Carbamazepine	Continue breast-feeding; adverse effects possible (severe skin reaction reported in one infant); monitor infant for drowsiness.
Carbimazole	Amount in milk may be sufficient to affect neonatal thyroid function; therefore, the lowest effective dose should be used; at the same time the fetal development should be monitored.
Ceftriaxone	Excreted in low concentrations; safe in usual dosage; monitor infant
Chloramphenicol	Continue breast-feeding; use alternative drug if possible; may cause bone marrow toxicity in infant; concentration in milk usually insufficient to cause "gray syndrome"
Chloroquine	At doses used for malaria prophylaxis, amount in milk probably too small to be harmful and inadequate for reliable protection against malaria in the breast-fed infant; avoid breast-feeding when used for rheumatic disease
Chlorphenamine	Safe in usual dosage; monitor infant for drowsiness
Chlorpromazine	Continue breast-feeding; adverse effects possible; monitor infant for drowsiness
Ciprofloxacin	Continue breast-feeding; use alternative drug if possible; high concentrations in breast milk
Clindamycin	Amount probably too small to be harmful but bloody diarrhea reported in 1 infant
Clomifene	May inhibit lactation

Medicine	Comment
Clomipramine	Small amount present in milk; continue breast-feeding; adverse effects possible; monitor infant for drowsiness
Cloxacillin	Trace amounts in milk; safe in usual dosage; monitor infant
Colchicine	Present in milk but adverse effects have not been reported; caution required because of its cytotoxicity effects
Contraceptives, oral	Combined oral contraceptives may inhibit lactation—use alternative method of contraception until weaning or for 6 months after birth; progestogen-only contraceptives do not affect lactation (preferably start 6 weeks after birth or later).
Dapsone	Although significant amount in milk, risk to infant very small; continue breast-feeding; monitor infant for jaundice
Deferoxamine	No information available; manufacturer advises use only if potential benefit outweighs risk
Diazepam	Continue breast-feeding; adverse effects possible; monitor infant for drowsiness.
Diclofenac	Amount too small to be harmful
Digoxin	Amount too small to be harmful
Dimercaprol	Avoid.
Doxycycline	Continue breast-feeding; use alternative drug if possible (absorption and therefore discoloration of teeth in infant probably usually prevented by chelation with calcium in milk)
Efavirenz	Women with HIV infection should be counseled about the risks of breast-feeding and advised, if it is possible, to avoid breast-feeding. When replacement feeding is acceptable, feasible, affordable, sustainable, and safe, breast-feeding should be avoided. Otherwise, exclusive breast-feeding is recommended during the first months of life and should then be discontinued as soon as feasible.
Emtricitabine	Breast-feeding recommended during first 6 months if no safe alternative to breast milk
Enalapril	Amount probably too small to be harmful
Enfuvirtide	See Efavirenz.
Enoxaparin	Manufacturer advises to avoid—no information available
Ephedrine	Irritation and sleep disturbances have been reported.
Ergocalciferol	Caution with high doses; may cause hypercalcemia in infant

Medicine	Comment
Ergotamine	Avoid; ergotism may occur in infant; repeated doses may inhibit lactation.
Erythromycin	Only small amounts in milk—not known to be harmful
Ethambutol	Amount too small to be harmful
Ethinylestradiol	May inhibit lactation; use alternative method of contraception
Ethosuximide	Significant amount in milk; continue breast-feeding; adverse effects possible; monitor infant for drowsiness
Etravirine	Women with HIV infection should be counseled about the risks of breast-feeding and advised, if it is possible, to avoid breast-feeding. When replacement feeding is acceptable, feasible, affordable, sustainable, and safe, breast-feeding should be avoided. Otherwise, exclusive breast-feeding is recommended during the first months of life and should then be discontinued as soon as feasible.
Fenofibrate	Manufacturer advises avoid—no information available
Fluconazole	Present in milk; safe in usual dosage; monitor infant
Flumazenil	Stop breast-feeding for 24 hours.
Fluorouracil	Discontinue breast-feeding.
Fluoxetine	Present in milk; manufacturer advises to avoid or use lowest effective dose
Fluphenazine	Amount excreted in milk probably too small to be harmful; continue breast-feeding; adverse effects possible; monitor infant for drowsiness
Fosamprenavir + ritonavir	See Efavirenz.
Furosemide	Amount too small to be harmful
Gentamicin	Amount probably too small to be harmful; monitor infant for thrush and diarrhea
Glibenclamide	Theoretical possibility of hypoglycemia in infant
Griseofulvin	No information available; avoid
Haloperidol	Amount present in milk probably too small to be harmful; continue breast-feeding; adverse effects possible; monitor infant for drowsiness
Halothane	Present in milk
Hydralazine	Present in milk but not known to be harmful; monitor infant
Hydrochlorothiazide	Continue breast-feeding; may inhibit lactation

Medicine	Comment
Hydrocortisone	Systemic effects in infant unlikely with maternal dose of less than equivalent of 40 mg prednisolone daily; monitor infant's adrenal function with higher doses
Hyoscine	Amount too small to be harmful
Ibuprofen	Amount too small to be harmful; short courses safe in usual doses
Imipramine	Amount of tricyclic antidepressants present in the milk are too small to be harmful.
Indinavir	See Efavirenz.
Insulin	Amount too small to be harmful
Iodine	Stop breast-feeding; danger of neonatal hypothyroidism or goiter; appears to be concentrated in milk
Isoflurane	Breast-feeding can be resumed as soon as mother has recovered sufficiently from anesthesia.
Isoniazid	Monitor infant for possible toxicity; theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother and infant
Ketoconazole	Manufacturer advises to avoid.
Lamivudine	See Efavirenz.
Lamivudine + nevirapine + zidovudine	See Efavirenz.
Lamivudine + zidovudine	See Efavirenz.
Levodopa + carbidopa	Present in milk; levodopa may inhibit lactation
Levonorgestrel	Combined oral contraceptives may inhibit lactation; use alternative method of contraception until weaning or for 6 months after birth; progestogen-only contraceptives do not affect lactation (preferably start 6 weeks after birth or later).
Levothyroxine	Amount too small to affect tests for neonatal hypothyroidism
Lidocaine	Amount too small to be harmful
Lopinavir + ritonavir	See Efavirenz.
Maraviroc	See Efavirenz.
Mebendazole	Amount too small to be harmful
Medroxyprogesterone acetate	Present in milk; no adverse effects reported (preferably start injectable contraceptive 6 weeks after birth or later)
Metformin	Present in milk but safe in usual doses; monitor infant

Medicine	Comment
Methadone	Withdrawal symptoms in infant; dose should be as low as possible and infant monitored to avoid sedation
Methotrexate	Breast-feeding contraindicated
Methyldopa	Amount too small to be harmful
Metoclopramide	Present in milk; adverse effects possible; monitor infant for adverse effects
Metoprolol	Infants should be monitored as there is a risk of possible toxicity due to beta blockade (and alpha blockade with labetalol or carvedilol), but the amount of most beta-blockers present in milk is too small to affect infants.
Metronidazole	Significant amount in milk; continue breast-feeding; avoid large doses; use alternative drug if possible
Midazolam	Present in milk—avoid breast-feeding for 24 hours after administration
Morphine	Short courses safe in usual doses; monitor infant
Mupirocin	No information available
Nalidixic acid	Risk to infant very small but 1 case of haemolytic anemia reported
Naloxone	No information available
Nelfinavir	See Efavirenz.
Neostigmine	Amount probably too small to be harmful; monitor infant
Nevirapine	See Efavirenz.
Nifedipine	Small amount in milk; continue breast-feeding; monitor infant
Nitrofurantoin	Only small amounts in milk but could be enough to produce hemolysis in G6PD-deficient infants
Norethisterone	Combined oral contraceptives may inhibit lactation; use alternative method of contraception until weaning or for 6 months after birth; progestogen-only contraceptives do not affect lactation (preferably start injectable contraceptive 6 weeks after birth or later).
Nortriptyline	The amounts of tricyclic antidepressants are too small to be harmful.
Nystatin	No information available, but absorption from gastrointestinal tract negligible
Omeprazole	Present in milk but not known to be harmful
Opium tincture	Caution during breast-feeding

Medicine	Comment
Paracetamol	Small amount present in milk; short courses safe in usual dosage; monitor infant
Penicillamine	No information available; manufacturer advises avoid unless potential benefit outweighs risk
Pentavalent antimony compounds	Avoid.
Pethidine	Present in milk but not known to be harmful
Phenobarbital	Continue breast-feeding; adverse effects possible; monitor infant for drowsiness
Phenoxymethylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Potassium iodide	Stop breast-feeding; danger of neonatal hypothyroidism or goiter; appears to be concentrated in milk
Povidone iodine	Avoid; iodine absorbed from vaginal preparations is concentrated in milk
Prednisolone	Systemic effects in infant unlikely with maternal dose of less than 40 mg prednisolone daily; monitor infant's adrenal function with higher doses
Primaquine	No information available; risk of hemolysis in G6PD-deficient infants
Procainamide	Present in milk; continue breast-feeding; monitor infant
Propofol	Breast-feeding can be resumed as soon as mother has recovered sufficiently from anesthesia.
Promethazine	Safe in usual dosage; monitor infant for drowsiness
Propranolol	Present in milk; safe in usual dosage; monitor infant
Pyrazinamide	Amount too small to be harmful
Pyridostigmine	Amount probably too small to be harmful
Pyrimethamine	Significant amount present in milk—avoid administration of other folate antagonists to infant; avoid breast-feeding during toxoplasmosis treatment
Quinine	Present in milk—continue breast-feeding and monitor infant; risk of hemolysis in G6PD deficient infants
Raltegravir	See Efavirenz.
Ranitidine	Significant amount present in milk, but not known to be harmful
Retinol	Theoretical risk of toxicity in infants of mothers taking large doses
Rifampicin	Amount too small to be harmful

Medicine	Comment
Ritonavir	See Lopinavir + ritonavir.
Salbutamol	Safe in usual dosage; monitor infant
Saquinavir	See Efavirenz.
Silver sulfadiazine	Continue breast-feeding; monitor infant for jaundice—small risk of kernicterus in jaundiced infants, particularly with long-acting sulphonamides, and of hemolysis in G6PD-deficient infants
Sodium stibogluconate	Small amount is harmful; not advised during breast-feeding
Stavudine	See Efavirenz.
Sulfadiazine	Monitor infant for jaundice—small risk of kernicterus in jaundiced infants and of hemolysis in G6PD-deficient infants; caution in ill or premature infants
Sulfadoxine + pyrimethamine	Monitor infant for jaundice—small risk of kernicterus in jaundiced infants and of hemolysis in G6PD-deficient infants (due to sulfadoxine); caution in ill or premature infants
Sulfamethoxazole + trimethoprim	Monitor infant for jaundice—small risk of kernicterus in jaundiced infants and of hemolysis in G6PD-deficient infants (due to sulfamethoxazole); caution in ill or premature infants.
Sulfasalazine	Use with caution; monitor infant for jaundice—small amounts in milk (one report of bloody diarrhea and rash); theoretical risk of neonatal hemolysis especially in G6PD-deficient infants; caution in ill or premature infants.
Tenofovir	See Efavirenz.
Terbinafine	Avoid—present in milk.
Tetracaine	No information available
Tetracycline	Continue breast-feeding; use alternative drug if possible (absorption and therefore discoloration of teeth in infant probably usually prevented by chelation with calcium in milk)
Thiopental	Present in milk—not known to be harmful
Tramadol	Amount probably too small to be harmful, but manufacturer advises to avoid
Trihexyphenidyl	Avoid.
Trimethoprim	Present in milk; safe in usual dosage; monitor infant
Valproic acid	Amount too small to be harmful
Verapamil	Amount too small to be harmful
Zidovudine	See Efavirenz.

APPENDIX D: Renal impairment

Reduced renal function may cause problems with drug therapy for the following reasons:

1. The failure to excrete a drug or its metabolites may produce toxicity.
2. The sensitivity to some drugs is increased even if the renal elimination is unimpaired.
3. The tolerance to adverse effects may be impaired.
4. The efficacy of some drugs may diminish.

The dosage of many drugs must be adjusted in patients with renal impairment to avoid adverse reactions and to ensure efficacy. The level of renal function below which the dose of a drug must be reduced depends on how toxic it is and whether it is eliminated entirely by renal excretion or is partly metabolized to inactive metabolites.

In general, all patients with renal impairment are given a *loading dose*, which is the same as the usual dose for a patient with normal renal function. *Maintenance doses* are adjusted to the clinical situation. The maintenance dose of a drug can be reduced either by reducing the individual dose, leaving the normal interval between doses unchanged, or by increasing the interval between doses without changing the dose. The interval extension method may provide the benefits of convenience and decreased cost, while the dose reduction method provides a more constant plasma concentration.

The following table lists drugs, in alphabetical order, for which specific information on use in renal impairment (including recommended doses) is available. Many drugs should be used with caution in renal impairment but no specific advice on dose adjustment is available; it is therefore important to also

refer to the individual drug entries. The recommendations are given for various levels of renal function as estimated by the glomerular filtration rate (GFR), usually measured by the creatinine clearance (best calculated from a 24-hour urine collection). The serum creatinine concentration is sometimes used instead as a measure of renal function but it is only a rough guide, even when corrected for age, sex, and weight by special nomograms.

Renal impairment is usually divided into 3 grades:

1. Mild: GFR, 20–50 ml/min or approximate serum creatinine, 150–300 micromole/L
2. Moderate: GFR, 10–20 ml/min or serum creatinine, 300–700 micromole/L
3. Severe: GFR, < 10 ml/min or serum creatinine, >700 micromole/L

When using the dosage guidelines, the following must be considered:

- Drug prescribing should be kept to a minimum.
- Nephrotoxic drugs should, if possible, be avoided in all patients with renal disease because the nephrotoxicity is more likely to be serious.
- It is advisable to determine renal function not only before but also during the period of treatment and adjust the maintenance dose as necessary.
- Renal function (GFR, creatinine clearance) declines with age, so that by the age of 80 it is half that in healthy young subjects. When prescribing for the elderly, assume at least a mild degree of renal impairment.
- Uremic patients should be observed carefully for unexpected drug toxicity. In these patients, the complexity of clinical status as well as other variables—for example, altered absorption, protein binding or metabolism, or liver function, and other drug therapy—precludes use of fixed drug dosage and an individualized approach is required.

Medicines to be avoided or used with caution in renal impairment

Medicine	Degree of impairment	Comment
Abacavir	Severe	Avoid
Acetazolamide	Mild	Avoid; metabolic acidosis
Acetylsalicylic acid	Severe	Avoid; sodium and water retention; deterioration in renal function; increased risk of gastrointestinal bleeding
Aciclovir	Mild	Reduce intravenous dose
Aciclovir	Moderate-to-severe	Reduce dose
Allopurinol	Moderate	100–200 mg daily; increased toxicity; rash
Allopurinol	Severe	100 mg on alternate days (max. 100 mg daily)
Aluminium hydroxide	Severe	Aluminium is absorbed and may accumulate. Note: Absorption of aluminum from aluminium salts is increased by citrates, which are contained in many effervescent preparations (such as effervescent analgesics).
Amidotrizoates	Mild	Reduce dose and avoid dehydration; nephrotoxic
Amoxicillin	Mild to severe	Risk of crystalluria with high doses
Amoxicillin	Severe	Reduce dose; rash more common and risk of crystalluria
Amoxicillin + clavulanic acid	Moderate to moderate	Risk of crystalluria with high doses (particularly during parenteral therapy); reduce dose if creatinine clearance less than

Medicine	Degree of impairment	Comment
		30 ml/min
Ampicillin	Severe	Reduce dose; rash more common
Atenolol	Mild to moderate	Reduce dose to a maximum 50 mg daily if creatinine clearance 15–35 ml/min
Atenolol	Severe	May reduce renal blood flow and adversely affect renal function; reduce dose to a maximum 25 mg daily if creatinine clearance less than 15 ml/min
Azithromycin	Moderate to severe to moderate	Neurotoxicity—high doses may cause convulsions
Benzathine benzylpenicillin	Severe	Neurotoxicity—high doses may cause convulsions
Benzylpenicillin	Severe	Maximum 6 g daily; neurotoxicity—high doses may cause convulsions
Captopril		ACE inhibitors should be used with caution and the response monitored; hyperkalemia and other side effects more common; the dose may need to be reduced.
Carbamazepine		Manufacturer advises caution.
Ceftriaxone	Severe	Maximum 2 g daily; also monitor plasma concentration if both severe renal impairment and hepatic impairment
Chloramphenicol	Severe	Avoid unless no alternative; dose-related depression of hematopoiesis
Chloroquine	Mild to moderate	Reduce dose in rheumatic

Medicine	Degree of impairment	Comment
		disease
Chloroquine	Severe	Reduce dose for malaria prophylaxis; avoid in rheumatic disease
Chlorphenamine	Severe	Dose reduction may be required.
Chlorpromazine	Severe	Start with small doses; increased cerebral sensitivity
Ciprofloxacin	Moderate	Use one-half the normal dose
Clindamycin		Plasma half-life prolonged—may need dose reduction
Cloxacillin	Severe	Reduce dose.
Colchicine	Moderate	Reduce dose.
Colchicine	Severe	Avoid; or if no alternative available reduce dose.
Deferoxamine		Metal complexes excreted by kidneys (in severe renal impairment dialysis increases rate of elimination)
Diazepam	Severe	Start with small doses; increased cerebral sensitivity
Diclofenac	Mild	Avoid in severe impairment.
Digoxin	Mild	Reduce dose; toxicity increased by electrolyte disturbances
Dimercaprol		Discontinue or use with extreme caution if impairment develops during treatment.
Doxycycline	Mild	Use with caution; avoid excessive doses.
Efavirenz	Severe	No information available; caution advised
Emtricitabine		Reduce dose; consult manufacturer's literature.

Medicine	Degree of impairment	Comment
Enalapril	Mild	Use with caution and monitor response; initial dose, 2.5 mg once daily if creatinine clearance less than 30 ml/min; hyperkalemia and other adverse effects more common
Ergometrine	Severe	Manufacturer advises to avoid.
Ergotamine	Moderate	Avoid; risk of renal vasoconstriction
Erythromycin	Severe	Maximum 1.5 g daily (ototoxicity)
Ethambutol	Mild	Reduce dose; if creatinine clearance less than 30 ml/min monitor plasma ethambutol concentration; optic nerve damage
Fenofibrate		Reduce dose to 134 mg daily if eGFR less than 60 ml/min/1.73m ² ; reduce dose to 67 mg daily if eGFR less than 20 ml/min/1.73m ² ; avoid if eGFR less than 15 ml/min/1.73m ²
Fluphenazine	Severe	Start with small doses; increased cerebral sensitivity
Furosemide	Moderate	May need high doses; deafness may follow rapid intravenous injection.
Gentamicin	Mild	Reduce dose; monitor plasma concentrations.
Glibenclamide	Severe	Avoid.
Haloperidol	Severe	Start with small doses; increased cerebral sensitivity
Heparin	Severe	Risk of bleeding increased
Hydralazine	Mild	Reduce dose if creatinine

Medicine	Degree of impairment	Comment
		clearance less than 30 ml/min
Hydrochlorothiazide	Moderate	Avoid; ineffective.
Ibuprofen	Mild	Use lowest effective dose and monitor renal function; sodium and water retention; deterioration in renal function possibly leading to renal failure
Ibuprofen	Moderate to severe	Avoid.
Imipramine		Use with caution in severe impairment.
Insulin	Severe	May need dose reduction; insulin requirements fall; compensatory response to hypoglycemia is impaired.
Iron + dextran		Avoid in acute renal failure.
Isoniazid	Severe	Maximum 200 mg daily; peripheral neuropathy
Lamivudine	Mild	Reduce dose; consult manufacturer's literature.
Lidocaine	Severe	Use with caution.
Lopinavir + ritonavir		Avoid oral solution due to propylene glycol content; use capsules with caution in severe impairment.
Magnesium hydroxide	Moderate	Avoid or reduce dose; increased risk of toxicity
Magnesium sulfate	Moderate	Avoid or reduce dose; increased risk of toxicity
Mannitol		Avoid unless test dose produces diuretic response.
Maraviroc		If eGFR less than 80 ml/min/ 1.73m^2 , consult product literature.

Medicine	Degree of impairment	Comment
Meglumine antimoniate		See Pentavalent antimony compounds.
Meglumine iotroxate	Moderate to severe	Increased risk of nephrotoxicity; avoid dehydration
Metformin	Mild	Avoid; increased risk of lactic acidosis
Methadone	Moderate to severe	Increased and prolonged effect; increased cerebral sensitivity
Methotrexate	Mild	Reduce dose; accumulates; nephrotoxic
Methotrexate	Moderate	Avoid.
Methyldopa	Moderate	Start with small dose; increased sensitivity to hypotensive and sedative effects
Metoclopramide	Severe	Avoid or use small dose; increased risk of extrapyramidal reactions
Midazolam		Start with small doses in severe impairment; increased cerebral sensitivity
Morphine	Moderate to severe	Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity
Mupirocine		Manufacturer advises caution when mupirocine ointment used in moderate or severe impairment because it contains macrogols (polyethylene glycol).
Nalidixic acid	Severe to moderate	Use with caution; avoid if eGFR less than 20 ml/min/1.73m ²
Nelfinavir		No information available; manufacturer advises caution
Neostigmine	Moderate	May need dose reduction

Medicine	Degree of impairment	Comment
Nitrofurantoin	Mild	Avoid; peripheral neuropathy; ineffective because of inadequate urine concentrations
Nortriptyline		Use with caution in severe renal impairment.
Penicillamine	Mild	Reduce dose and monitor renal function.
Pentavalent antimony compounds	Moderate	Increased adverse effects
Pentavalent antimony compounds	Severe	Avoid.
Pethidine	Moderate to severe	The effects of opioid analgesia are increased and prolonged and there is increased cerebral sensitivity when patients with renal impairment are treated with opioid analgesics; avoid use or reduce dose.
Phenobarbital	Severe	Avoid large doses.
Povidon iodine	Severe	Avoid regular application to inflamed or broken mucosa.
Potassium chloride	Moderate	Avoid routine use; high risk of hyperkalemia
Procainamide	Mild	Avoid or reduce dose.
Procaine benzylpenicillin	Severe	Neurotoxicity—high doses may cause convulsion
Propofol		Use with caution.
Propranolol	Severe	Start with small dose; higher plasma concentrations after oral administration; may reduce renal blood flow and adversely affect renal function
Quinine		Reduce parenteral maintenance dose for malaria treatment.
Ranitidine	Severe	Use half normal dose;

Medicine	Degree of impairment	Comment
		occasional risk of confusion
Ritonavir		See Lopinavir + ritonavir.
Saquinavir	Severe	Dose adjustment possibly required
Sodium chloride	Severe	Avoid.
Sodium hydrogen carbonate	Severe	Avoid; specialized role in some forms of renal disease
Sodium stibogluconate		Avoid in severe renal failure.
Spironolactone	Mild	Monitor plasma potassium concentrations; high risk of hyperkalemia in renal impairment
Spironolactone	Moderate	Avoid.
Stavudine	Mild	20 mg twice daily (15 mg if body weight less than 60 kg)
Stavudine	Moderate to severe	20 mg once daily (15 mg if body weight less than 60 kg)
Streptomycin	Mild	Reduce dose; monitor plasma concentrations.
Sulfamethoxazole + trimethoprim	Mild	Use one half of normal dose if creatinine clearance 15–30 ml/min; avoid if creatinine clearance less than 15 ml/min and if plasma sulfamethoxazole concentration cannot be monitored.
Sulfasalazine	Moderate	Risk of toxicity including crystalluria—ensure high fluid intake
Sulfasalazine	Severe	Avoid.
Terbinafine		Use one-half of normal dose if eGFR less than 50 ml/min/1.73m ² and no suitable

Medicine	Degree of impairment	Comment
		alternative available.
Thiopental	Severe	Caution in severe impairment
Tramadol		The effects of opioid analgesia are increased and prolonged and there is increased cerebral sensitivity when patients with renal impairment are treated with opioid analgesics; avoid use or reduce dose.
Trihexyphenidyl		Use with caution in severe renal impairment.
Trimethoprim	Mild	Use one-half of normal dose after 3 days if creatinine clearance is 15–30 ml/min
Trimethoprim	Moderate to severe	Use one-half normal of dose if creatinine clearance is less than 15 ml/min; avoid if creatinine clearance less than 10 ml/min (unless plasma trimethoprim concentration monitored).
Valproic acid	Mild to moderate	Reduce dose.
Valproic acid	Severe	Alter dosage according to free serum valproic acid concentration.
Zidovudine	Severe	Reduce dose; manufacturer advises oral dose of 300–400 mg daily in divided doses or intravenous dose of 1 mg/kg 3–4 times daily.

APPENDIX E: Hepatic impairment

Liver disease may alter the response to drugs. However, the hepatic reserve appears to be large and liver disease has to be severe before important changes in drug metabolism take place. The ability to eliminate a specific drug may or may not correlate with the liver's synthetic capacity for substances such as albumin or clotting factors, which tends to decrease as hepatic function declines. Unlike renal disease, where estimates of renal function based on creatinine clearance correlate with parameters of drug elimination such as clearance and half-life, routine liver function tests do not reflect actual liver function but are rather markers of liver cellular damage.

The altered response to drugs in liver disease can include all or some of the following changes:

- Impaired intrinsic hepatic eliminating (metabolizing) capacity due to lack of or impaired function of hepatocytes
- Impaired biliary elimination due to biliary obstruction or transport abnormalities (for example, rifampicin is excreted in the bile)
- Unchanged and may accumulate in patients with intrahepatic or extrahepatic obstructive jaundice
- Impaired hepatic blood flow due to surgical shunting, collateral circulation, or poor perfusion with cirrhosis and portal hypertension
- Altered volume of distribution of drugs due to increased extracellular fluid (ascites, edema) and decreased muscle mass
- Decreased protein binding and increased toxicity of drugs highly bound to proteins (for example, phenytoin) due to impaired albumin production
- Increased bioavailability through decreased first-pass metabolism
- Decreased bioavailability due to malabsorption of fats in cholestatic liver disease

In severe liver disease, increased sensitivity to the effects of some drugs can further impair cerebral function and may precipitate *hepatic encephalopathy* (for example, morphine). *Edema* and *ascites* in chronic liver disease may be exacerbated by drugs that cause fluid retention (for example, acetylsalicylic acid, ibuprofen, prednisolone, dexamethasone). Usually, drugs are metabolized without injury to the liver. A few drugs cause dose-related hepatotoxicity. However, most hepatotoxic reactions to drugs are rare but tend to be unpredictable. In patients with impaired liver function, the dose-related hepatotoxic reaction may occur at lower doses and the unpredictable reactions seem to occur more frequently. Both should be avoided.

Information to aid prescribing in hepatic impairment is included in the following table. The table contains only those drugs that need dose adjustment. However, non-inclusion in the table does not automatically imply safety, as for many drugs data about safety are absent; it is therefore important to also refer to the individual drug entries.

Medicines to be avoided or used with caution in liver disease

Medicine	Comment
Abacavir	Avoid in moderate hepatic impairment unless essential; avoid in severe hepatic impairment.
Acetylsalicylic acid	Avoid in severe hepatic impairment; increased risk of gastrointestinal bleeding
Allopurinol	Reduce dose;
Aluminium hydroxide	In patients with fluid retention avoid antacids containing large amounts of sodium; also avoid those causing constipation (can precipitate coma).
Aminophylline	Reduce dose.
Amitriptyline	Sedative effect increased (avoid in severe liver

Medicine	Comment
	disease)
Amlodipine	Half-life prolonged—may need dose reduction; consider initial dose of 2.5 mg.
Amoxicillin + clavulanic acid	Monitor liver function in liver disease; cholestatic jaundice reported either during or shortly after treatment—more common in patients over the age of 65 years and in males; duration of treatment should not usually exceed 14 days.
Atazanavir + ritonavir	Manufacturer advises caution in mild impairment; avoid in moderate-to-severe impairment.
Atorvastatin	Statins should be used with caution in those with a history of liver disease and avoided in active liver disease or when there are unexplained persistent elevations in serum transaminases.
Azithromycin	Avoid; jaundice reported
Bromocriptine	In severe impairment may need dose reduction
Bupivacaine	Avoid (or reduce dose) in severe liver disease.
Carbamazepine	Metabolism impaired in advanced liver disease
Carbimazole	In mild-to-moderate impairment use with caution; in severe cases avoid.
Ceftriaxone	Reduce dose and monitor plasma concentration if both hepatic and severe renal impairment.
Chloramphenicol	Avoid if possible—increased risk of bone marrow depression; reduce dose and monitor plasma chloramphenicol concentration.
Chlorphenamine	Sedation inappropriate in severe liver disease—avoid
Chlorpromazine	Can precipitate coma; hepatotoxic
Ciprofloxacin	Hepatic impairment reported
Clindamycin	Reduce dose

Medicine	Comment
Clomifene	Avoid in severe liver disease
Clomipramine	Sedative effects increased; avoid in severe liver disease
Cloxacillin	Cholestatic jaundice may occur up to several weeks after treatment has been stopped; administration for more than 2 weeks and increasing age are risk factors
Contraceptives, oral	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy.
Diazepam	Can precipitate coma.
Diclofenac	NSAIDs should be used with caution in patients with hepatic impairment; there is an increased risk of gastrointestinal bleeding and fluid retention. NSAIDs should be avoided in severe liver disease.
Doxycycline	Avoid (or use with caution).
Efavirenz	In mild-to-moderate liver disease, monitor for dose related side effects (for example, CNS effects) and monitor liver function; avoid in severe hepatic impairment.
Enalapril	Closely monitor liver function in patients with hepatic impairment.
Enfuvirtide	Manufacturer advises caution—no information available; chronic hepatitis B or C (possibly greater risk of hepatic side effects)
Ergometrine	Avoid in severe liver disease.
Ergotamine	Avoid in severe hepatic impairment; toxicity may be increased.
Erythromycin	May cause idiosyncratic hepatotoxicity.
Ethinylestradiol	Avoid; see also Contraceptives, oral.
Etravirine	Manufacturer advises caution in moderate impairment; avoid in severe impairment—no information available; greater risk of hepatic side effects in chronic hepatitis B or C.
Fenofibrate	Avoid.

Medicine	Comment
Flumazenil	Carefully titrate dose.
Fluorouracil	Caution advised; dose reduction may be required
Fluphenazine	Can precipitate coma; hepatotoxic
Fosamprenavir + ritonavir	Protease inhibitors should be used with caution in patients with chronic hepatitis B or C (increased risk of hepatic side effects).
Furosemide	Hypokalemia may precipitate coma (use potassium sparing diuretic to prevent this); increased risk of hypomagnesemia in alcoholic cirrhosis
Glibenclamide	Increased risk of hypoglycemia in severe liver disease; avoid or use small dose; can produce jaundice
Griseofulvin	Avoid in severe liver disease.
Haloperidol	Can precipitate coma
Halothane	Avoid if history of unexplained pyrexia or jaundice following previous exposure to halothane.
Heparin	Reduce dose in severe liver disease.
Hydralazine	Reduce dose.
Hydrochlorothiazide	Avoid in severe liver disease; hypokalemia may precipitate coma (potassium-sparing diuretic can prevent this); increased risk of hypomagnesemia in alcoholic cirrhosis
Ibuprofen	Increased risk of gastrointestinal bleeding and can cause fluid retention; avoid in severe liver disease
Imipramine	Tricyclic antidepressants are preferable to MAOIs in hepatic impairment but sedative effects are increased. They should be avoided in severe liver disease.
Indinavir	Increased risk of nephrolithiasis; reduce dose to 600 mg every 8 hours in mild-to-moderate hepatic impairment; not studied in severe

Medicine	Comment
	impairment
Iron dextran	Not advised in severe impairment
Isoniazid	Use with caution; monitor liver function regularly and particularly frequently in the first 2 months.
Ketoconazole	Avoid.
Levonorgestrel	Caution in active liver disease and recurrent cholestatic jaundice
Lidocaine	Avoid (or reduce dose) in severe liver disease.
Lopinavir + ritonavir	Avoid oral solution because of propylene glycol content; avoid capsules in severe hepatic impairment.
Magnesium hydroxide	Avoid in hepatic coma if risk of renal failure.
Magnesium sulfate	Avoid in hepatic coma if risk of renal failure.
Maraviroc	Manufacturer advises to use with caution.
Medroxyprogesterone acetate	Avoid in active liver disease and if history of pruritus during pregnancy.
Meglumine antimoniate	See Pentavalent antimony compounds.
Metformin	Withdraw if tissue hypoxia likely—manufacturers advise to avoid.
Methadone	Avoid or reduce dose—may precipitate coma.
Methotrexate	Dose-related toxicity; avoid in non-malignant conditions (for example, rheumatic disorders); avoid for all indications in severe hepatic impairment.
Methyldopa	Manufacturer advises caution in history of liver disease; avoid in active liver disease.
Metoprolol	Reduce dose in severe impairment.
Metoclopramide	Reduce dose.
Metronidazole	In severe liver disease, reduce total daily dose to one-third and give once daily.
Midazolam	Use with caution; can precipitate coma.
Morphine	Avoid or reduce dose—may precipitate coma.
Nalidixic acid	Manufacturer advises caution in liver disease.
Nelfinavir	No information available; manufacturer advises

Medicine	Comment
	caution.
Nevirapine	Caution in moderate hepatic impairment; avoid in severe hepatic impairment.
Nifedipine	Reduce dose in severe liver disease.
Nitrofurantoin	Cholestatic jaundice and chronic active hepatitis reported
Norethisterone	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy.
Nortriptyline	Tricyclic antidepressants are preferable to MAOIs in hepatic impairment but sedative effects are increased. They should be avoided in severe liver disease.
Omeprazole	Not more than 20 mg daily should be needed.
Paracetamol	Dose-related toxicity—avoid large doses
Pentavalent antimony compounds	Increased risk of liver damage and hepatic failure in pre-existing liver disease
Pethidine	Avoid or reduce dose; may precipitate coma.
Phenobarbital	May precipitate coma
Prednisolone	Adverse effects more common
Procainamide	Avoid or reduce dose
Promethazine	Avoid—may precipitate coma in severe liver disease; hepatotoxic
Propofol	Use with caution.
Propranolol	Reduce oral dose.
Pyrazinamide	Monitor hepatic function—idiosyncratic hepatotoxicity more common; avoid in severe hepatic impairment.
Raltegravir	Manufacturer advises caution in severe impairment—no information available
Ranitidine	Increased risk of confusion; reduce dose
Rifampicin	Impaired elimination; monitor liver function; avoid or do not exceed 8 mg/kg daily
Ritonavir	See Lopinavir + ritonavir.
Saquinavir	Manufacturer advises caution in moderate hepatic impairment; avoid in severe

Medicine	Comment
	impairment.
Sodium stibogluconate	Use with caution in hepatic failure.
Sulfamethoxazole + trimethoprim	Manufacturer advises avoid in severe liver disease.
Suxamethonium	Prolonged apnea may occur in severe liver disease due to reduced hepatic synthesis of plasma cholinesterase.
Terbinafine	Manufacturer advises to avoid— elimination reduced.
Thiopental	Reduce dose for induction in severe liver disease.
Tramadol	Opioid analgesics may precipitate coma in patients with hepatic impairment; avoid use or reduce dose.
Trihexyphenidyl	Use with caution.
Valproic acid	Avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months).
Verapamil	Reduce oral dose.
Zidovudine	Accumulation may occur.

APPENDIX F: Table of specific antidotes for some toxic agents and overdose of some medicines

Toxic agent/ drug overdose	Specific antidote	Dose and route of administration
Acetaminophen (paracetamol)	N-acetylcysteine	ADULT and CHILD; IV infusion 150 mg/kg in 15 minutes, then 50 mg/kg in 4 hours, then 100 mg/kg in 16 hours ADMINISTRATION: Dilute requisite dose in glucose intravenous infusion solution, 5%, as follows: ADULT and

Toxic agent/ drug overdose	Specific antidote	Dose and route of administration
		CHILD over 12 years: Initially 200 ml given over 15 minutes, then 500 ml over 4 hours, then 1 L over 16 hours. CHILD under 12 years with a body weight over 20 kg: Initially 100 ml given over 15 minutes, then 250 ml over 4 hours, then 500 ml over 16 hours. CHILD under 12 years with a body weight under 20 kg: Initially 3 ml/kg given over 15 minutes, then 7 ml/kg over 4 hours, then 14 ml/kg over 16 hours. Note: Manufacturer may recommend other infusion fluids, but glucose solution, 5%, is preferable.
Anticholinesterases (for example, organophosphates and insecticides)	Atropine	IM or IV (depending on severity of poisoning). ADULT: 2 mg (CHILD: 0.020 mg/kg) every 5–10 minutes until skin becomes flushed and dry, pupils dilate, and tachycardia develops.
Anticholinesterases (for example, organophosphates and insecticides)	Pralidoxime	IV infusion. ADULT and CHILD: Initially 30 mg/kg over 20 minutes followed by 8 mg/kg/hour; usual maximum dose 12 g in 24 hours Note: The loading dose may be administered <i>by intravenous injection</i> (diluted to a concentration of 50 mg/ml with water for injections) over at least 5 minutes if pulmonary edema is present or if it is not practical to administer an intravenous infusion.
Benzodiazepines	Flumazenil	IV injection 200 micrograms over 15 seconds, then if needed 100 micrograms in 60-second intervals; usual range of dose is 300–600

Toxic agent/ drug overdose	Specific antidote	Dose and route of administration
		micrograms. Maximum dose 1 mg (in ICU 2 mg); if no response with repeated dose the causative factor should be questioned. If vertigo returns 100–400 micrograms by IV infusion in 1 hour and adjusted based on consciousness of the patients.
Calcium-channel blockers	Calcium chloride or calcium gluconate	ADULT: 30 ml calcium gluconate 10%, or 10 ml calcium chloride, 10%, over 15–20 minutes. After 3 doses close monitoring of calcium should be done to prevent hypercalcemia.
Carbon monoxide	Oxygen, hyperbaric oxygen	High flow of 100% oxygen through tightened face mask
Cyanide	Hydroxocobalamin	By IV infusion. ADULT: 5 g over 15 minutes; a second dose of 5 g can be given over 15 minutes or 30 minutes and adjusted based on consciousness and stability CHILD: 70 mg/kg (max. dose 5 g) in 15 minutes, a second dose of 70 mg/kg can be given over 15 minutes up to 2 hours depending of the severity of toxicity and stability of patient.
Heparin	Protamine sulfate	Overdosage with intravenous injection of unfractionated heparin, by intravenous injection (rate not exceeding 5 mg/minute): 1 mg neutralizes 80–100 units heparin when given within 15 minutes of heparin; if longer time than 15 minutes since heparin given, less protamine is required (consult product literature for

Toxic agent/ drug overdose	Specific antidote	Dose and route of administration
		details) as heparin is rapidly excreted; maximim 50 mg
Insulin, beta-blocker	Glucagon	–Hypoglycemia due to insulin, subcutaneous, IM or IV: ADULT and CHILD over 8 years (or over 25 kg body weight): 1 mg; CHILD less than 8 years (or less than 25 kg body weight): 500 microgram. If no response within 10 minutes IV glucose in large vein should be administered –Beta blockers overdosage: Glucagon IV 2–10 mg (CHILD: 50–150 microgram/kg, max. dose 10 mg). – Unlicensed indication and dose: in glucose, 5% (with precautions to protect the airway in case of vomiting) followed by an IV infusion of 50 microgram/kg/hour.
Iron	Deferoxamine	–Acute poisoning with iron, slow IV infusion. ADULT and CHILD: Initially 15 mg/kg/hour, reduced dose after 4–6 hours so that total dose does not exceed 80 mg/kg in 24 hours –Chronic iron overload, subcutaneous or IV infusion. ADULT and CHILD: Lowest effective dose (usually within a range of 20–60 mg/kg/day) for 4–7 days in a week
Isoniazid	Pyridoxine (vitamin B6)	–In prevention of risk of ototoxicity and peripheral neuropathy: By mouth. ADULT: 10 mg daily. –Treatment of overdosage: By mouth 50 mg 3 times daily until the signs relieved

Toxic agent/ drug overdose	Specific antidote	Dose and route of administration
Lead	Calcium disodium edetate	IV infusion. ADULT and CHILD up to 40 mg/kg: 2 times/day for up to 5 days; repeated if necessary after interval of 48 hours
Lead and copper	Penicillamine	–Lead poisoning: By mouth 1–2 g daily in divided doses before meal (up to the confirmation that the urine excretion of lead is stabilized to less than 500 micrograms/day). CHILD : 20 mg/kg in divided doses –Wilson disease, by mouth. ADULT : 1.5–2 g daily in divided doses before meals (max. 2 g daily for 1 year), thereafter 0.75–1g daily; ELDERLY : 20 mg/kg daily in divided doses adjusted according to response; CHILD : Up to 20 mg/kg daily in divided doses (min. 500 mg daily)
Mercury and arsenic	Dimercaprol	IM administration. ADULT and CHILD : 2.5–3 mg/kg every 4 hours for 2 days, then 3 mg/kg 2–4 times on third day, afterward 3 mg/kg 1–2 times daily for 10 days or until recovery
Methanol, ethylene glycol	(Ethyl alcohol orally) or Ethanol 10% with 5% Dextrose IV	IV or by mouth. Ethanol can be used with caution. Treatment of overdose of ethylene glycol and methanol should be done after consulting the specialist.
Methemoglobinemia	Methylene blue	Slow IV injection over several minutes. ADULT and CHILD : Single dose of 1–2 mg/kg; may be repeated after 1 hour if needed
Neostigmine	Atropine	The muscarinic effects of neostigmine is reversible by competitive neuromuscular blocking, which is achieved by intravenous

Toxic agent/ drug overdose	Specific antidote	Dose and route of administration
		administration of 0.6 to 1.2 mg; dose for under 12 years child is 20 microgram/kg (max. dose is 1.2 mg)
Opioids	Naloxone	IV injection. ADULT: 0.4–2 mg repeated at intervals of 2–3 minutes up to a maximum of 10 mg. Question diagnosis if respiratory function does not improve. CHILD: 10 microgram/kg; a subsequent dose of 100 microgram/kg may be given if no response. Note: Naloxone hydrochloride may be administered in the same doses by intramuscular or subcutaneous injection , but only if the intravenous route is not feasible (slower onset of action).
Opioids	Naltrexone	ADULT over 18 years (only start in specialist clinic): Initially 25 mg, then 50 mg daily. Total weekly dose (350 mg) may be divided and given on 3 days of the week for improved compliance (for example, 100 mg on Monday and 100 mg on Wednesday and 150 mg on Friday); maximum duration 4 months.
Snake venom	Snake antivenom	Relates to use of specific toxin; refer to publication of the manufacturer.
Scorpion venom	Scorpion antivenom	Dilute 1 vial of antivenom in 100 ml saline and administer it over 30 minutes through IV , if symptoms are still present administer the second vial after 1–3 hours as before.
Warfarin, warfarin-based anticoagulants and super-	Vitamin K1 (phytomenadione)	In massive hemorrhage: Stop warfarin; administration of

Toxic agent/ drug overdose	Specific antidote	Dose and route of administration
warfarin based rodenticide		phytomenadione (vitamin K1) 5–10 mg by slow IV , administration of dehydrated prothrombin complex (II, VII, IX and X factors), 30–50 unit/kg (in case of unavailability of dehydrated prothrombin complex use fresh frozen plasma 15 ml/kg, but it has less effect)
	Activated charcoal/ universal antidote	Poisoning (reduction of absorption), by mouth, as soon as possible after ingestion of poison. ADULT: 50–100 g as a single dose; INFANT: 1 g/kg as a single dose; CHILD: 1–12 years, 25 g as a single dose (50 g in severe poisoning). Poisoning (active elimination), by mouth: ADULT: 50 g every 4 hours (in case of intolerance 25 g every 2 hours); INFANT: 1 g/kg every 4–6 hours; CHILD over 1 year: 25–50 g every 4–6 hours



Adverse Drug Reactions (ADR) Form
 Email address: pvcenterafg@gmail.com
 Phone number: 0202104659

Ministry of Public Health
 General Directorate of Pharmaceutical Affairs
 Avicenna Pharmaceutical Institute
 Pharmacovigilance Center

Serial Number ()

Date of filling the form (/ /)

A. Patient Information										
1. Patient Initial: _____		Age: _____		Sex: Male ☐ Female ☐		Weight: _____ Kg		Phone: _____		
P. Address: House number: _____		St: _____		village: _____		Dt/ward: _____		Province: _____		
Breastfeeding/Pregnancy (if applicable) Yes ☐ No ☐										
B. Suspected Adverse Event (Drug Reaction, Medication Error, Drug Quality)										
2. Date & time Event started: / / (time_____)			3. Date & time Event stopped: / / (time_____)			4. Discontinuation of suspected drug: Yes ☐ No ☐				
5. Reaction abated after drug stopped or dose reduced: Yes ☐ No ☐					6. Reaction reappeared after reintroduction: Yes ☐ No ☐					
7. Reaction Details: _____										
8. Reaction Management details: _____										
9. Outcome of Reaction: Recovered completely: Yes ☐ No ☐ (If not recovered) what is the outcome? Death ☐ (please write the Date / /) Continuing ☐										
10. Reaction Seriousness: Not serious reaction ☐ Disability ☐ Life threatening ☐ Congenital anomaly ☐ Prolonged hospitalization ☐ Death ☐										
11. Other medical history (renal/hepatic dysfunction etc.): _____										
12. Relevant Laboratory Tests: _____ Relevant Laboratory Results: _____										
C. Suspected Drug (s)										
13. Name (brand/generic)/form	Manufacturer	Batch/Lot Number	Expiry date	Dose & strength	Route used	Frequency	Indication	Therapy Dates (if known)		
								Started	Stopped	Dose reduced
1.										
2.										
3.										
4.										
14. Concomitant drug (s) Name (brand/generic)/form	Manufacturer	Batch/Lot Number	Expiry date	Dose & strength	Route used	Frequency	Indication	Therapy Dates (if known)		
								Started	Stopped	Dose reduced
1.										
2.										
D. Reporter (to be kept Confidential)										
15. Name of the reporter: _____			Email address (if available): _____			Phone number: _____				
Profession: _____			Date of Reporting / /			Signature: _____				
16. Report received by (name and signature of the person who receives the form): _____								Date Report received: / /		

The following guideline is to aid the reporter in filling out the Adverse Drug Reaction Form:

A. Personal information regarding the patient

1. **Patient initials:** The first letters of patient's first and last name. For example if the name of the patient is **Abdul Majeed Farooqi** then the initials would be **A.M.F.**
 - Age: The exact age of the patient based on the register of the hospital or stated by the care giver of patient (may be stated as Year, Month or day)
 - Sex: Check either male or female.
 - Weight: The weight of the patient in kilograms.
 - Register number: If an ADR case is reported from any health facility where the patient is registered before reporting.
 - Phone: Include the patient's phone number (if available) or the phone number of the care giver or nearest relative by whom we can easily reach the patient.
 - Address: The existing residence of the patient including street, village, district or ward and province.

B. Information regarding the suspected event

2. **Date and time event started:** The date when the first signs/symptoms of suspected event occurred
3. **Date and time event stopped:** Indicate the date when the suspected reaction lasted
4. **Discontinuation of suspected drug:** Was use of the drug discontinued after the event occurred? Check yes or no.
5. **Reaction abated after drug stopped or dose reduced:** Check yes or no if the reaction abated after the drug was stopped or once the dose was reduced (if the reaction stopped is the same day, please indicate the duration by hour)
6. **Reaction reappeared after reintroduction:** Indicate whether the reaction reappeared once the drug was restarted (if applicable)
7. **Reaction details:** Describe the adverse reaction, including any signs and symptoms that occurred
8. **Reaction Management details:** Describe what clinical interventions took place to treat or manage the event
9. **Outcome of Reaction:** What was the outcome of the event? If the patient recovered fully, the date should be clearly written. Otherwise check one of the other boxes. If occurred from the event, include the date as well or check continues in case when no recovery and death are occurred.
10. **Reaction Seriousness:** Indicate the severity of the event. Check the appropriate box

Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening

- Cancers and congenital anomalies or birth defects should be regarded as serious
 - Medical events that would be regarded as serious if they had not responded to acute treatment should also be considered serious
 - The term "severe" is used to describe the intensity (severity) of an event, as in the grading "mild", "moderate", and "severe"; thus a severe skin reaction need not be life threatening
11. **Other medical history:** Refers to any other illnesses or allergies not recorded
 12. **Relevant Laboratory Tests/Relevant Laboratory Results:** If applicable, indicate any laboratory tests that were performed, including the dates and the results.

C. Suspected Drug (s):

13. **Name of suspect drug:** includes the entire information on name, dosage form, and any other information about the drug which is suspected to be caused the event. Include information as possible with their starting date of treatment and stopping along with their indications.
14. **Concomitant drug:** The drug (s) name, dosage form, and any other information which are responsible for developing the event after available investigations.

D. Reporter (to be kept Confidential)

15. **Name of the reporter:** The reporter name that is filling out this form including an email address, phone number, profession, date, and his/her signature.
16. **Report received by:** The person who receives the completed form should write his/her name with sign and date of receiving and send the form to the related bodies.

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