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Abbreviations

ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
AV	atrioventricular
BCG	Bacille Calmette–Guérin (vaccine)
BP	British Pharmacopoeia
BSA	body surface area
CNS	central nervous system
CSF	cerebrospinal fluid
DOTS	directly observed treatment, short-course
DMARD	disease-modifying agents in rheumatoid disorders
ECG	electrocardiogram
EEG	electroencephalogram
G6PD	glucose 6-phosphate dehydrogenase
GFR	glomerular filtration rate
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
INR	international normalized ratio
MB	multibacillary leprosy
MDI	metered dose inhaler
MDR-TB	multidrug-resistant tuberculosis
NSAIM	non-steroidal anti-inflammatory medicine
PB	paucibacillary leprosy
PTB	pulmonary tuberculosis
spp.	species
SSRI	selective serotonin reuptake inhibitor
TB	tuberculosis
USP	United States Pharmacopeia
WHO	World Health Organization

Introduction

In 1995, the WHO Expert Committee on the Use of Essential Drugs recommended that WHO develop a Model Formulary which would complement the WHO Model List of Essential Drugs (the "Model List"). It was considered that such a WHO Model Formulary would be a useful resource for countries wishing to develop their own national formulary. The WHO Model Formulary was first published in August 2002.

In this edition, we have reverted to the structure and sections used in the WHO Model List. Although this may not always reflect ideal therapeutic categories, it has been done as part of the process of updating the entire WHO Medicines Library, which now has one interlinked structure that includes the formulary information as well as other information about the listed medicines. Countries or organizations which choose to adapt the Model Formulary for their own purposes may wish to adjust the structure to suit their needs. The WHO Model List and the WHO Model Formulary are available electronically on the WHO Essential Medicines Library web site (http://www.who.int/emlib/); search facilities provide easy access to relevant information.

An electronic version of the WHO Model Formulary is also available, intended as a starting point for developing national or institutional formularies. National or institutional committees can use the text of the WHO Model Formulary for their own needs either by adapting the text, or by adding or deleting entries to align the formulary to their own list of essential medicines.

This edition of the WHO Model Formulary is fully compatible with the 15th WHO Model List of Essential Medicines as recommended by the WHO Expert Committee on the Selection and Use of Essential Medicines at its meeting of March 2007. For a list of the more significant changes made to the WHO Model List at this time see Changes to the WHO Model List of Essential Medicines (page vii).

Comments and suggestions for corrections or changes are very welcome and should be sent to:

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Changes to the WHO Model List of Essential Medicines

Changes made to the 14th WHO Model List (2005) to produce the 15th WHO Model List (2007) are listed below:

Other changes

Section 8.2	Cytotoxic medicines were marked for review at the next meeting of the Expert Committee.
Section 8.4	The note for medicines used in palliative care was updated.
Section 19.3	The Committee revised the note on the selection of vaccines and updated the WHO Model List to include all vaccines for which there is a SAGE recommendation or a WHO position paper.
Section 21	Ophthalmological preparations were marked for review at the next meeting of the Expert Committee.

Additions

Section 2.2	Morphine, prolonged-release tablet: 10 mg; 30 mg; 60 mg.
Section 5	Carbamazepine, chewable tablet: 100 mg; 200 mg; and oral liquid: 100 mg/5 ml.
	Phenobarbital, injection: 200 mg/ml.
	Phenytoin, chewable tablet: 50 mg and oral liquid: 25–30 mg/5 ml.
	Valproic acid, crushable tablet: 100 mg and oral liquid: 200 mg/5 ml.
Section 6.2.1	Cefazolin, powder for injection: 1 g in vial (as sodium salt).
Section 6.2.4	Isoniazid, scored tablet: 50 mg. Pyrazinamide, dispersible tablet: 150 mg and scored tablet: 150 mg.
	Rifampicin + isoniazid + ethambutol, fixed-dose combination tablet: 150 mg + 75 mg + 275 mg.
Section 6.4.2.1	Emtricitabine capsules 200 mg and oral liquid 10 mg/ml.
Section 6.4.2.2	Efavirenz tablet 600 mg.

Section 6.4.2.1	Tenofovir disoproxil fumarate, tablet : 300 mg.
New unnumbered section:	**Fixed-dose combinations of antiretrovirals:**
	Efavirenz + emtricitabine + tenofovir, tablet: 600 mg + 200 mg + 300 mg.
	Emtricitabine + tenofovir, tablet: 200 mg + 300 mg.
	Stavudine + lamivudine + nevirapine, tablet: 30 mg + 150 mg + 200 mg.
	Zidovudine + lamivudine, tablet : 300 mg + 150 mg.
	Zidovudine + lamivudine + nevirapine, tablet: 300 mg + 150 mg + 200 mg.
Section 6.4.3	**Other antivirals (new section):** Ribavirin, injection for intravenous administration: 800 mg; 1000 mg in 10-ml phosphate buffer solution and oral solid dosage form: 200 mg; 400 mg; 600 mg.
Section 6.5.2	Paromomycin, solution for intramuscular injection: 750 mg/2 ml (as sulfate).
Section 6.5.3	Artesunate, injection: 60 mg.
Section 11.2	Human normal immunoglobulin, for intravenous administration: 5%; 10% protein solution and for intramuscular administration: 16% protein solution.
Section 12.6	Simvastatin, tablet: 5 mg; 10 mg; 20 mg; 40 mg.
Section 18.3.2	Medroxyprogesterone acetate + estradiol cypionate, injection: 25 mg + 5 mg.
Section 18.3.5	**Implantable contraceptives (new section):** Levonorgestrel-releasing implant, two-rod: each containing 75 mg levonorgestrel.
Section 19.3	Cholera, hepatitis A, *Haemophilus influenzae* type b, Japanese encephalitis, pneumococcal, rotavirus, and varicella vaccines.
Section 21.1	Aciclovir, ointment: 3% W/W.
Section 24.2.1	Fluoxetine, tablet or capsule: 20 mg.
Section 25.2	**Other medicines acting on the respiratory tract (new section):** Caffeine citrate, injection: 20 mg/ml and oral liquid: 20 mg/ml.
Section 27	Retinol, capsule: 50,000 IU; 100,000 IU (as palmitate).

Amendments to dosage strengths and forms

Section 12.2	Epinephrine (adrenaline) injection: changed to 100 micrograms/ml in 10-ml ampoule.
Section 13.2	Neomycin sulfate + bacitracin, ointment: changed to neomycin sulfate, 5 mg + bacitracin zinc 250 IU/g.
Section 13.4	Aluminium diacetate, solution: changed to 5%.
Section 19.2	Antivenom sera, changed to antivenom immunoglobulin.

Deletions

Section 6.2.4	Ciprofloxacin and levofloxacin for the treatment of multidrug resistant-TB.
Section 6.5.3.1	Chloroquine, injection: 40 mg/ml in 5-ml ampoule.
Section 6.5.5.1	Pentamidine, powder for injection: 300 mg.
Section 8.2	Chlormethine, powder for injection: 10 mg.
	Levamisole, tablet: 50 mg.
Section 14.2	Iopanoic acid, tablet: 500 mg.
	Propyliodone, oily suspension: 500–600 mg/20 ml ampoules.
Section 21.1	Idoxuridine, ointment: 0.2% and solution: 0.1%.

Moved from complementary to core list

Section 6.5.3.1	Artemether, oily injection: 80 mg/ml in 1-ml ampoule.
	Artesunate, tablet: 50 mg.
	Doxycycline, tablet or capsule: 100 mg.
	Mefloquine, tablet: 250 mg.
	Sulfadoxine + pyrimethamine, tablet: 500 mg + 25 mg.
Section 6.5.5.1	Eflornithine, injection: 200 mg.
	Pentamidine; powder for injection: 200 mg.

General advice to prescribers

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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 cost. *The guide to good prescribing*; Geneva: World Health Organization; 1994, provides undergraduates with important tools for training in the process of rational prescribing.

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 integrating 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 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 for treatment of 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*

Selecting the correct group of drugs

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

Selecting the drug from the chosen group

The selection process must consider benefit/risk/cost information. This step is based on evidence about 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 and 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.

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.

Prescription writing

As 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).

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).

Monitoring treatment

Evaluation of the follow-up and the outcome of treatment allows the stopping of it (if the patient's problem is solved) or its reformulation it when necessary. This step gives rise to important information about the effects of drugs, contributing to the building up of 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 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 to dissolve. Enteric-coated drugs have been known to pass through the gastrointestinal tract intact. In drugs with a narrow therapeutic to 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 size or shape. Yet adult weights vary 2- to 3-fold, 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 much higher doses being administered than necessary; in such cases, dose should be calculated from an ideal weight, related to height and age. Nomograms are available to allow body surface values to be calculated from 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 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.

Pharmacodynamic variables

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

Disease variables

Both liver disease and kidney disease can have major effects on drug response, chiefly through the 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, anaesthetic 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 in 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 to 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 drug "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 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 to 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 hypoglycaemia 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 thus encouraged to record and report to their national pharmacovigilance centre any unexpected adverse effects with any drug in order to 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 which predispose to ADRs.

Extremes of age

The very old and the very young are more susceptible to ADRs. Drugs which commonly cause problems in the elderly include hypnotics, diuretics, non-steroidal anti-inflammatory drugs, antihypertensives, psychotropics, and digoxin.

All children, and 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 (grey baby syndrome), antiarrhythmics (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 1) may occur between drugs which compete for the same receptor or which 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 which 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 which modify the effects of a drug may involve non-prescription drugs, non-medicinal chemical agents, and social drugs such as alcohol, marijuana, tobacco, and traditional remedies, as well as 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 that isoform. Alterations in the rate of the metabolic reaction catalysed by that isoform are likely to have effects on the pharmacokinetics of the drug.

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 Ciclosporin 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 preparation, 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 it. Many countries have separate regulations for prescriptions for controlled drugs such as opioid analgesics.

The following guidelines will help to 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. Generic substitution is allowed in some countries. 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 which 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 counselling 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 millilitres (abbreviated as "ml") or litres (preferably not abbreviated since the letter "l" could be confused with the figure "1").

Narcotics and controlled substances

The prescribing of a medicinal product that is liable to abuse 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

PRESCRIPTION

Dr B Who
Geneva
Switzerland
Tel: +41 22 791 2111

Date:

Name of patient: _____

Address: _____

_____

_____

_____

Date of birth: **Sex:**

Treatment:

For use by the dispensary

SECTION 1:
Anaesthetics

1.1 General anaesthetics and oxygen 16

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1.3 Preoperative medication and sedation for short-term procedures 26

This section describes drugs used in anaesthesia. The reader is referred to *WHO model prescribing information, Drugs used in anaesthesia*. Geneva, World Health Organization, 1989, for more detailed information.

To produce a state of prolonged full surgical anaesthesia reliably and safely, a variety of drugs is needed. Special precautions and close monitoring of the patient are also required. Anaesthetic 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) anaesthetic technique is used, it is essential that facilities for intubation and mechanically-assisted ventilation are available. A full preoperative assessment is required including, if necessary, appropriate fluid replacement.

Anaesthesia 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 to 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 anaesthetist is 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).

1.1 General anaesthetics and oxygen

Intravenous agents

Intravenous anaesthetics may be used alone to produce anaesthesia for short surgical procedures but are more commonly used for induction only. They can produce apnoea and hypotension and thus facilities for adequate resuscitation must be available. They are contraindicated if the anaesthetist 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 hypovolaemic patients.

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

Anaesthesia 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. Subanaesthetic 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 orthopaedic procedures. Recovery from ketamine anaesthesia 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 anaesthetics, 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 anaesthesia with ether [no longer included on the 15th WHO Model List]. 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 are 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 anaesthetized with halothane within a short period of time.

Inhalational gases

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

Oxygen should be added routinely during anaesthesia 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 coloured 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 coloured white. Cylinders containing nitrous oxide and oxygen mixtures should be similarly labelled, and the neck coloured white and blue.

Halothane

Inhalation.

Volatile liquid.

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

Uses: induction and maintenance of anaesthesia.

Contraindications: history of unexplained jaundice or pyrexia following previous exposure to halothane; family history of malignant hyperthermia; raised cerebrospinal fluid pressure; porphyria.

Precautions: anaesthetic history should be carefully taken to determine previous exposure and previous reactions to halothane (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 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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.

Ketamine

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

Uses: induction and maintenance of anaesthesia; analgesia for painful procedures of short duration.

Contraindications: thyrotoxicosis; hypertension (including pre-eclampsia); history of cerebrovascular accident, cerebral trauma, intracerebral mass or haemorrhage, or other cause of raised intracranial pressure; eye injury and increased intraocular pressure; psychiatric disorders, particularly hallucinations; porphyria.

Precautions: supplementary analgesia often required in surgical procedures involving visceral pain pathways (morphine may be used but addition of nitrous oxide will often suffice); administer an antisialogogue to prevent excessive salivation leading to respiratory difficulties; during recovery, patient must remain undisturbed but under observation; pregnancy (Appendix 2); **interactions**: Appendix 1.

SKILLED TASKS. Warn patient not to perform skilled tasks, for example, operating machinery or driving for 24 hours and also to avoid alcohol for 24 hours.

Dose:

Induction, *by intramuscular injection*, **ADULT** and **CHILD**, 6.5–13 mg/kg (10 mg/kg usually produces 12–25 minutes of anaesthesia); maintenance, 50–100% of induction dose as required.

Induction, *by intravenous injection* over at least 1 minute, **ADULT** and **CHILD**, 1–4.5 mg/kg (2 mg/kg usually produces 5–10 minutes of anaesthesia); maintenance, 50–100% of induction dose as required.

Induction, *by intravenous infusion* of a solution containing 1 mg/ml, **ADULT** and **CHILD**, total induction dose 0.5–2 mg/kg; maintenance (using microdrip infusion), 10–45 micrograms/kg/minute, 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 possibly accompanied by irrational behaviour (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.

Nitrous oxide

Inhalation.

Inhalation gas.

Uses: maintenance of anaesthesia in combination with other anaesthetic agents (halothane, ether, or ketamine) and muscle relaxants; analgesia for obstetric practice, for emergency management of injuries, during postoperative physiotherapy and for refractory pain in terminal illness.

Contraindications: demonstrable collection of air in pleural, pericardial or peritoneal space; intestinal obstruction; occlusion of middle ear; arterial air embolism; decompression sickness; chronic obstructive airway disease, emphysema.

Precautions: minimize exposure of staff; pregnancy (Appendix 2); **interactions:** Appendix 1.

Dose:

Anaesthesia, **ADULT** and **CHILD**, nitrous oxide mixed with 25–30% oxygen.

Analgesia, 50% nitrous oxide mixed with 50% oxygen.

Adverse effects: nausea and vomiting; after prolonged administration megaloblastic anaemia and depressed white cell formation; peripheral neuropathy.

Oxygen

Inhalation (medicinal gas).

Uses: to maintain an adequate oxygen tension in inhalational anaesthesia.

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

Precautions: interactions: Appendix 1.

Dose:

Concentration of oxygen in inspired anaesthetic 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.

Thiopental

Powder for injection: 0.5 g; 1.0 g (sodium salt) in ampoule.

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

Uses: induction of anaesthesia prior to administration of inhalational anaesthetic; anaesthesia of short duration.

Contraindications: inability to maintain airway; hypersensitivity to barbiturates; cardiovascular disease; dyspnoea 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 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

SKILLED TASKS. Warn patient not to perform skilled tasks, for example, operating machinery or driving for 24 hours and also 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 the elderly or debilitated patients), followed by a further 100–150 mg if necessary according to response after 30–60 seconds; or up to 4 mg/kg (maximum 500 mg); **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 anaesthetics

Drugs used for conduction anaesthesia (also termed local or regional anaesthesia) act by causing a reversible block to conduction along nerve fibres. Local anaesthetics are used very widely in dental practice, for brief and superficial interventions, for obstetric procedures, and for specialized techniques of regional anaesthesia 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 anaesthetic 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 anaesthesia. Lower-segment caesarean section can also be performed under local infiltration anaesthesia. The local anaesthetic 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 anaesthetic, and prolongs its effect. Care is necessary when using epinephrine for this purpose since, in excess, it may produce ischaemic necrosis. It should **not** be added to injections used in digits or appendages.

Surface anaesthesia

Topical preparations of **lidocaine** are available and topical eye drop solutions of **tetracaine** (section 21.3) are used for local anaesthesia of the cornea and conjunctiva.

Regional block

A regional nerve block can provide safe and effective anaesthesia 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 anaesthesia

This is one of the most useful of all anaesthetic 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

Injection: 0.25%; 0.5% (hydrochloride) in vial.
Injection for spinal anaesthesia: 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution.

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

Uses: infiltration anaesthesia; peripheral and sympathetic nerve block; spinal anaesthesia; postoperative pain relief.

Contraindications: adjacent skin infection or inflamed skin; concomitant anticoagulant therapy; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patients.

Precautions: respiratory impairment; hepatic impairment (Appendix 5); epilepsy; porphyria; myasthenia gravis; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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); 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 labour, 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 labour, using 0.25–0.5% solution, **ADULT** (female), up to 100 mg (maximum 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 anaesthesia.

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 anaesthesia occasionally complicated by urinary retention, faecal incontinence, headache, backache, or loss of perineal sensation; transient paraesthesia and paraplegia very rare.

Ephedrine

Injection: 30 mg (hydrochloride)/ml in 1-ml ampoule.

Ephedrine hydrochloride is a complementary medicine.

Uses: prevention of hypotension during delivery under spinal or epidural anaesthesia.

Precautions: hyperthyroidism; diabetes mellitus; ischaemic heart disease, hypertension; angle-closure glaucoma; renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

Dose:

To prevent hypotension during delivery under spinal anaesthesia, *by slow intravenous injection* of solution containing 3 mg/ml, **ADULT**, 3–6 mg (maximum single dose, 9 mg), repeated if necessary every 3–4 minutes (maximum cumulative dose, 30 mg).

Adverse effects: anorexia, hypersalivation, nausea, vomiting; tachycardia (also in fetus), arrhythmias, anginal pain, vasoconstriction with hypertension, vasodilation with hypotension; dyspnoea; headache, dizziness, anxiety, restlessness, confusion, tremor; difficulty in micturition; sweating, flushing; changes in blood glucose concentration.

Lidocaine

Injection: 1%; 2% (hydrochloride) in vial.
Injection for spinal anaesthesia: 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution.
Topical forms: 2–4% (hydrochloride).

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

Uses: surface anaesthesia of mucous membranes; infiltration anaesthesia; peripheral and sympathetic nerve block; dental anaesthesia; spinal anaesthesia; intravenous regional anaesthesia; arrhythmias (section 12.2).

Contraindications: adjacent skin infection, inflamed skin; concomitant anticoagulant therapy; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patients.

Precautions: bradycardia, impaired cardiac conduction; severe shock; respiratory impairment; renal impairment (Appendix 4); hepatic impairment (Appendix 5); epilepsy; porphyria; myasthenia gravis; avoid (or use with great care) solutions containing epinephrine (adrenaline) for ring block of digits or appendages (risk of ischaemic necrosis); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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 anaesthesia of pharynx, larynx, trachea, using 4% solution, **ADULT**, 40–200 mg (1–5 ml).

Surface anaesthesia of urethra, using 4% solution, **ADULT**, 400 mg (10 ml).

Spinal anaesthesia, 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 anaesthesia, using 2% solution with epinephrine, **ADULT**, 20–100 mg (1–5 ml).

NOTE. 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 anaesthesia.

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 anaesthesia occasionally complicated by urinary retention, faecal incontinence, headache, backache, or loss of perineal sensation; transient paraesthesia and paraplegia very rare.

Lidocaine + epinephrine (adrenaline)

Dental cartridge: 2% (hydrochloride) + epinephrine 1:80 000.

Injection: 1%; 2% (hydrochloride) + epinephrine 1:200 000 in vial.

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

Uses: surface anaesthesia of mucous membranes; infiltration anaesthesia; peripheral and sympathetic nerve block; dental anaesthesia; spinal anaesthesia; intravenous regional anaesthesia; arrhythmias (section 12.2).

1.3 Preoperative medication and sedation for short-term procedures

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

Sedatives improve the course of subsequent anaesthesia 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 antiemetic properties as well as a sedative effect, is of particular value in children.

A potent analgesic such as **morphine** (section also 2.2) 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 anaesthesia. 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

Injection: 1 mg (sulfate) in 1-ml ampoule.

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; the elderly; ulcerative colitis, diarrhoea; hyperthyroidism; heart failure, or hypertension; pyrexia; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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 anaesthesia, **CHILD**, 20 micrograms/kg (maximum 600 micrograms); *by subcutaneous* or *intramuscular injection*, **ADULT**, 300–600 micrograms 30–60 minutes before induction; **CHILD**, 20 micrograms/kg (maximum, 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 (maximum, 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

Injection: 5 mg/ml in 2-ml ampoule.
Tablet: 5 mg.

Drug subject to international control under the Convention on Psychotropic Substances (1971).

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

Uses: premedication before major or minor surgery; sedation with amnesia for endoscopic procedures and surgery under local anaesthesia; in combination with pethidine [not included on the 15th WHO Model List], when anaesthetic 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 apnoea; 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); hepatic impairment (Appendix 5) or renal failure (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); close observation required until full recovery after sedation; porphyria; **interactions**: Appendix 1.

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 are 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.

Morphine

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

See section 2.2.

Promethazine

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

Uses: premedication prior to surgery; antiemetic (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 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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)

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs) 31

2.2 Opioid analgesics 35

2.3 Medicines used to treat gout 39

2.4 Disease-modifying agents used in rheumatoid disorders (DMARDs) 40

Pain may be modified by psychological factors and attention to these is essential in pain management. 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 (section 5) for trigeminal neuralgia and amitriptyline (section 24.2.1) for diabetic neuropathy and postherpetic neuralgia.

Non-opioid analgesics (section 2.1) are particularly suitable for musculoskeletal pain whereas the opioid analgesics (section 2.2) are more suitable for moderate to severe visceral pain. Non-opioid analgesics which 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 antirheumatic drugs (DMARDs) may favourably influence the disease process (section 2.4). The pain and inflammation of an acute attack of gout is treated with a NSAIM (section 2.3) or colchicine [not included on the 15th WHO Model List]; a xanthine oxidase inhibitor (section 2.3) is used for long-term control of gout.

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

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

Acetylsalicylic acid

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 (section 7.1), transient musculoskeletal pain, and dysmenorrhoea, and for reducing fever. Although it may be used in higher doses in the management of pain and inflammation of rheumatoid arthritis, other NSAIMs are preferred because they are likely to be better tolerated. Acetylsalicylic acid is also used for its antiplatelet properties (section 12.5). 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 (section 7.1), and for reducing fever, including post-immunization pyrexia. Paracetamol is particularly useful in patients in whom salicylates or other NSAIMs 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 irritant to the stomach. Unlike acetylsalicylic acid and other NSAIMs, 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.

NSAIMs (non-steroidal anti-inflammatory medicines)

NSAIMs, including **ibuprofen**, have analgesic, anti-inflammatory, and antipyretic properties. In single doses, NSAIMs 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 NSAIMs 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 NSAIMs but its anti-inflammatory properties are weaker. Diclofenac and naproxen (neither of which is included on the 15th WHO Model List) 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 NSAIMs caution should be exercised in the treatment of the elderly, in allergic disorders, and during pregnancy and breastfeeding. In patients with renal, cardiac or hepatic impairment, the dose should be kept as low as possible and renal function should be monitored. NSAIMs 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 commonest adverse effects are generally gastrointestinal including nausea, vomiting, diarrhoea, and dyspepsia; hypersensitivity reactions including anaphylaxis, bronchospasm, and rash have been reported, as has fluid retention.

Acetylsalicylic acid

Suppository: 50–150 mg.

Tablet: 100–500 mg.

Uses: mild to moderate pain including dysmenorrhoea, 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 NSAIM; children and adolescents under 16 years (to reduce risk of Reye syndrome, see also notes above); previous or active peptic ulceration; haemophilia and other bleeding disorders; not for treatment of gout.

Precautions: asthma, allergic disease; renal impairment (Appendix 4); hepatic impairment (Appendix 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3); elderly; G6PD-deficiency; dehydration; **interactions**: Appendix 1.

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.

Mild to moderate pain, pyrexia, *by rectum*, **ADULT**, 600–900 mg inserted every 4 hours if necessary; maximum, 3.6 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 haemorrhage); also other haemorrhage including subconjunctival; hearing disturbances such as tinnitus (rarely deafness), vertigo, confusion, hypersensitivity reactions including angioedema, bronchospasm, and rash; increased bleeding time; rarely oedema, myocarditis and blood disorders (particularly thrombocytopenia).

Ibuprofen

Tablet: 200 mg; 400 mg.

Uses: pain and inflammation in rheumatic disease and other musculoskeletal disorders including juvenile arthritis; mild to moderate pain including dysmenorrhoea and headache; pain in children; acute migraine attack (section 7.1).

Contraindications: hypersensitivity (including asthma, angioedema, urticaria, or rhinitis) to acetylsalicylic acid or any other NSAIM; active peptic ulceration.

Precautions: renal impairment (Appendix 4); hepatic impairment (Appendix 5); preferably avoid if history of peptic ulceration; cardiac disease; elderly; pregnancy (Appendix 2) and breastfeeding (Appendix 3); coagulation defects; allergic disorders; **interactions**: Appendix 1.

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, 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.

Adverse effects: gastrointestinal disturbances including nausea, diarrhoea, dyspepsia, ulceration, and haemorrhage; hypersensitivity reactions including rash, angioedema and bronchospasm; headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, tinnitus, photosensitivity,

haematuria; fluid retention (rarely precipitating congestive heart failure in the elderly), raised blood pressure, renal failure; rarely hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (Stevens-Johnson syndrome), toxic dermal necrolysis (Lyell syndrome), colitis and aseptic meningitis.

Paracetamol

Oral liquid: 125 mg/5 ml.
Suppository: 100 mg.
Tablet: 100–500 mg.

Uses: mild to moderate pain including dysmenorrhoea and headache; pain relief in osteoarthritis and soft tissue lesions; pyrexia including post-immunization pyrexia; acute migraine attack (section 7.1).

Precautions: hepatic impairment (Appendix 5); renal impairment (Appendix 4); alcohol dependence; breastfeeding (Appendix 3); overdosage: section 4.2; **interactions**: Appendix 1.

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 the 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**, 0.5–1g; **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; 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 (see also section 8.4). 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 overdosage

Opioids cause coma, respiratory depression and pinpoint pupils. **Naloxone** is a specific antidote indicated if there is coma or bradypnoea. 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 are only partially reversed by naloxone. Methadone 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 overdosage with large doses; a withdrawal syndrome may occur in neonates of opioid-dependent mothers.

Codeine

Tablet: 30 mg (phosphate).

Drug subject to international control under the Single Convention on Narcotic Drugs (1961).

Uses: mild to moderate pain; diarrhoea (section 17.5.3).

Contraindications: respiratory depression, obstructive airways disease, acute asthma attack; where risk of paralytic ileus.

Precautions: renal impairment (Appendix 4) and hepatic impairment (Appendix 5); dependence; pregnancy (Appendix 2) and breastfeeding (Appendix 3); overdosage: section 4.2; **interactions**: Appendix 1.

Dose:

Mild to moderate pain, *by mouth*, **ADULT**, 30–60 mg every 4 hours when necessary; maximum, 240 mg daily; **CHILD** 1–12 years, 0.5–1 mg/kg every 4–6 hours when needed; maximum, 240 mg daily.

Adverse effects: constipation particularly troublesome in long-term use; dizziness, nausea, vomiting; difficulty with micturition; ureteric or biliary spasm; dry mouth, headaches, sweating, facial flushing; in therapeutic doses, codeine is much less liable than morphine to produce tolerance, dependence, euphoria, sedation, or other adverse effects.

Morphine

Injection: 10 mg (morphine hydrochloride or morphine sulfate) in 1-ml ampoule.
Oral liquid: 10 mg (morphine hydrochloride or morphine sulfate)/5 ml.
Tablet: 10 mg (morphine sulfate).
Tablet (prolonged-release): 10 mg; 30 mg; 60 mg (morphine sulfate).

Drug subject to international control under the Single Convention on Narcotic Drugs (1961).

Uses: severe pain (acute and chronic); myocardial infarction, acute pulmonary oedema; adjunct during major surgery and postoperative analgesia.

Contraindications: avoid in acute respiratory depression, acute alcoholism, and where risk of paralytic ileus; also avoid in raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma.

Precautions: renal impairment (Appendix 4) and hepatic impairment (Appendix 5); 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; pregnancy

(Appendix 2) and breastfeeding (Appendix 3); overdosage: section 4.2; **interactions:** Appendix 1.

Dose:

Acute pain, *by subcutaneous injection* (not suitable for oedematous 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 mouth* (immediate-release tablets) or *by subcutaneous injection* (not suitable for oedematous patients) or *by intramuscular injection,* **ADULT**, 5–20 mg regularly every 4 hours; dose may be increased according to need; oral dose should be approximately double corresponding intramuscular dose; *by mouth* (sustained-release tablets), titrate dose first using immediate-release preparation, then every 12 hours according to daily morphine requirement (see note above).

Myocardial infarction, *by slow intravenous injection* (2 mg/minute), **ADULT**, 10 mg followed by a further 5–10 mg if necessary; elderly or debilitated patients, reduce dose by half.

Acute pulmonary oedema, *by slow intravenous injection* (2 mg/minute), **ADULT**, 5–10 mg.

NOTE. The doses stated above refer equally to morphine sulfate and morphine hydrochloride. Sustained-release capsules designed for once daily administration are also available [not included on the 15th WHO Model List]; consult manufacturer's literature. Dosage requirements should be reviewed if the brand of controlled-release preparation is altered.

PATIENT ADVICE. Sustained-release tablets should be taken at regular intervals and not on an as-needed basis for episodic or breakthrough pain. Sustained-release tablets should not be crushed.

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.

2.3 Medicines used to treat gout

Acute gout

Acute attacks of gout are usually treated with high doses of a **NSAIM** such as indomethacin (150–200 mg daily in divided doses); ibuprofen has weaker anti-inflammatory properties than other NSAIMs and is therefore less suitable for treatment of gout. Salicylates, including acetylsalicylic acid are also not suitable because they may increase plasmaurate concentrations. Colchicine [not included on the 15th WHO Model List] is an alternative for those patients in whom NSAIMs 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 NSAIM or colchicine should be used as a prophylactic and continued for at least 1 month after the hyperuricaemia 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

Tablet: 100 mg.

Uses: prophylaxis of gout; prophylaxis of hyperuricaemia 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 litres daily; pregnancy (Appendix 2) and breastfeeding (Appendix 3); renal impairment (Appendix 4); hepatic impairment (Appendix 5); withdraw treatment if rash occurs, reintroduce if rash is mild but discontinue immediately if it recurs; **interactions**: Appendix 1.

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 NSAIM (not ibuprofen or a salicylate) or colchicine from the start of allopurinol treatment and continue for at least 1 month after correction of hyperuricaemia.

Prophylaxis of hyperuricaemia 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 afterwards; **CHILD** under 15 years, 10–20 mg/kg daily (maximum, 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, paraesthesia, neuropathy, gynaecomastia, and blood disorders (including leukopenia, thrombocytopenia, haemolytic anaemia, and aplastic anaemia).

2.4 Disease-modifying agents used in rheumatoid disorders (DMARDs)

The process of cartilage and bone destruction which occurs in rheumatoid arthritis may be reduced by the use of a diverse group of medicines known as DMARDs (disease-modifying antirheumatic 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 a NSAIM 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 extra-cellular 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 (section 18.1) 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 which has failed to respond to other antirheumatic 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 (see section 8.2), may be needed to control vasculitis.

Azathioprine

Tablet: 50 mg.

Azathioprine is a complementary medicine for rheumatoid arthritis.

Uses: rheumatoid arthritis in cases that have failed to respond to chloroquine or penicillamine; psoriatic arthritis; transplant rejection (section 8.1); inflammatory bowel disease (section 17.3).

Contraindications: hypersensitivity to azathioprine or mercaptopurine

Precautions: monitor for toxicity throughout treatment; monitor full blood counts frequently; hepatic impairment (Appendix 5); renal impairment (Appendix 4); elderly (reduce dose); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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 1.5–2.5 mg/kg daily in divided doses, adjusted according to response; maintenance dose, 1–3 mg/kg daily; consider withdrawal if no improvement within 3 months.

Adverse effects: hypersensitivity reactions requiring immediate and permanent withdrawal include malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension, and interstitial nephritis; dose-related bone marrow suppression; liver impairment, cholestatic jaundice; hair loss and increased susceptibility to infections and colitis in patients also receiving corticosteroids; nausea; rarely pancreatitis and pneumonitis; hepatic veno-occlusive disease; also herpes zoster infection.

Chloroquine

Tablet: 100 mg; 150 mg (as phosphate or sulfate).

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).

Contraindications: psoriatic arthritis.

Precautions: monitor visual acuity throughout treatment and warn patient to report immediately any unexplained visual disturbances; hepatic impairment; renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); neurological disorders including epilepsy; severe gastrointestinal disorders; G6PD deficiency; elderly; may exacerbate psoriasis and aggravate myasthenia gravis; porphyria; **interactions:** Appendix 1.

Dose:

Administered on expert advice.

NOTE. All doses 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 anaemia); 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 overdosage.

Methotrexate

Tablet: 2.5 mg (as sodium salt).

Methotrexate is a complementary medicine for rheumatoid arthritis.

Uses: rheumatoid arthritis; malignant disease (section 8.2).

Contraindications: pregnancy (Appendix 2) and breastfeeding (Appendix 3); immunodeficiency syndromes; significant pleural effusion or ascites.

Precautions: monitor throughout treatment (including blood counts and hepatic and renal function tests); renal impairment (avoid if moderate or severe, see also Appendix 4); hepatic impairment (avoid if severe; see also Appendix 5); reduce dose or withdraw if acute infection develops; advise men and women to use contraception during, and for at least 6 months after, treatment; peptic ulceration, ulcerative colitis, diarrhoea, ulcerative stomatitis; advise patient to avoid self-medication with salicylates or other NSAIMs; warn patient with rheumatoid arthritis to report cough or dyspnoea; **interactions**: Appendix 1.

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 diarrhoea occur, stop treatment; renal failure; skin reactions, alopecia, osteoporosis, arthralgia, myalgia, ocular irritation; precipitation of diabetes.

Penicillamine

Capsule or tablet: 250 mg.

Penicillamine is a complementary medicine for rheumatoid arthritis.

Uses: severe rheumatoid arthritis; copper and lead poisoning (section 4.2).

Contraindications: lupus erythematosus.

Precautions: monitor throughout treatment (including blood counts and urine tests); renal impairment (Appendix 4); concomitant nephrotoxic drugs (increased risk of toxicity); pregnancy (Appendix 2) and breastfeeding (Appendix 3); 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; **interactions**: Appendix 1.

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 anaemia; proteinuria, rarely haematuria (withdraw immediately); haemolytic anaemia, 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

Tablet: 500 mg.

Sulfasalazine is a complementary medicine for rheumatoid arthritis.

Uses: severe rheumatoid arthritis; ulcerative colitis and Crohn 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; renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); history of allergy; G6PD deficiency; slow acetylator status; **interactions**: Appendix 1.

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.

Adverse effects: nausea, diarrhoea, headache, loss of appetite; fever; blood disorders (including Heinz body anaemia, megaloblastic anaemia, leukopenia, neutropenia, and thrombocytopenia); hypersensitivity reactions (including rash, urticaria, erythema multiforme (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 oedema); stomatitis, parotitis; ataxia, aseptic meningitis, vertigo, tinnitus, alopecia, peripheral neuropathy, insomnia, depression, hallucinations; renal effects (including proteinuria, crystalluria, and haematuria); oligospermia; rarely acute pancreatitis, hepatitis; urine may be coloured orange; some soft contact lenses may be stained.

SECTION 3:
Antiallergics and medicines used in anaphylaxis

The H_1-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 one 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

oedema, hypertension, and hypokalaemia), osteoporosis, spontaneous fractures, skin thinning, increased susceptibility to infection, mental disturbances, and diabetes mellitus. For further information on the disadvantages of corticosteroids, see section 18.1.

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 oedema, 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, antibacterials (especially penicillins), iron injections, heparin, and neuromuscular blocking drugs. Acetylsalicylic acid and other non-steroidal anti-inflammatory medicines (NSAIMs) 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 which 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 (see section 1.1).

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 dopamine (see section 12.4), intravenous aminophylline [not included on the 15th WHO Model List] or an injected or nebulized bronchodilator, such as salbutamol (see section 25.1).

Steps in the management of anaphylaxis

1. **Sympathomimetic**

   Epinephrine (adrenaline), *by intramuscular injection* using epinephrine injection 1:1000, **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), 6–12 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 inadequate, epinephrine (adrenaline) *by slow intravenous injection* using epinephrine injection 1:10 000 (given at a rate of 1 ml/minute), **ADULT**, 500 micrograms (5 ml); **CHILD**, 10 micrograms/kg (0.1 ml/kg), given over several minutes.

2. **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 (maximum 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 litre 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

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

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

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 2); and breastfeeding (Appendix 3); renal impairment (Appendix 4); hepatic impairment (Appendix 5); epilepsy; **interactions**: Appendix 1.

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery or driving.

Dose:

Allergy, *by mouth*, **ADULT,** 4 mg every 4–6 hours (maximum, 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 (maximum 6 mg daily); **CHILD** 6–12 years, 2 mg every 4–6 hours (maximum 12 mg daily).

Allergic reactions, anaphylaxis (adjunct), *by subcutaneous, intramuscular, or intravenous injection*, **ADULT,** 10–20 mg (maximum 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.

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.

Dexamethasone

Injection: 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule.

Uses: adjunct in the emergency treatment of anaphylaxis; short-term suppression of inflammation in allergic disorders; for other indications, see section 18.1.

Contraindications: untreated systemic infection (unless condition life-threatening); administration of live virus vaccines.

Precautions: increased susceptibility to, and severity of, infection; activation or exacerbation of tuberculosis, amoebiasis and strongyloidiasis; risk of severe chickenpox in non-immune patients (varicella-zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; corneal perforation; for further precautions relating to long-term use of corticosteroids see section 18.1.

Dose:

Allergy (short-term use), *by mouth*, **ADULT,** usual range 0.5–10 mg daily as a single dose in the morning; **CHILD,** 10–100 micrograms/kg daily.

Anaphylaxis (adjunct), *by slow intravenous injection* or *infusion* (as dexamethasone phosphate), **ADULT,** 0.5–24 mg; **CHILD,** 200–400 micrograms/kg.

Adverse effects: nausea, dyspepsia, malaise, hiccups; hypersensitivity reactions including anaphylaxis; perineal irritation after intravenous administration; for adverse effects associated with low-dose, long-term corticosteroid treatment see section 18.1.

Epinephrine (adrenaline)

Injection: 1 mg (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 labour; 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 1.

Dose:

Anaphylaxis, *by intramuscular* or *subcutaneous injection* of 1:1000 epinephrine injection, see Steps in the Management of Anaphylaxis 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 for doses.

Adverse effects: tachycardia and arrhythmias, hypertension, tremor, anxiety, sweating, nausea, vomiting, weakness, hyperglycaemia, dizziness and pulmonary oedema have all been reported; headache common.

Hydrocortisone

Powder for injection: 100 mg (as sodium succinate) in vial.

Uses: adjunct in the emergency treatment of anaphylaxis; inflammatory skin conditions (section 13.3); inflammatory bowel disease (section 17.3); 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.

Adverse effects: for adverse effects associated with long-term corticosteroid treatment, see section 18.1.

Prednisolone

Tablet: 5 mg; 25 mg.

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

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, amoebiasis, and strongyloidiasis; risk of severe chickenpox in non-immune patients (varicella-zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; corneal perforation; 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.

SECTION 4:
Antidotes and other substances used in poisonings

4.1 Non-specific 56

4.2 Specific 58

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

4.1 Non-specific

Ideally, all patients who show features of poisoning should be admitted to 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 which are prolonged or recurrent may be controlled by intravenous diazepam (see section 5).

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 only practical in hospital and are only suitable for a small number of patients and a limited number of poisons. Methods include haemodialysis and haemoperfusion. 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 only be considered 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 and 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 is most effective if administered within one 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 which are toxic in small amounts, for example, antidepressants. Furthermore, repeated doses of activated charcoal enhance the faecal elimination of some drugs (that undergo enterohepatic or enteroenteric recycling) several hours after ingestion and after they have been absorbed, for example, phenobarbital and theophylline.

Charcoal, activated

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 diarrhoea; pneumonitis (due to aspiration).

4.2 Specific

Paracetamol overdosage

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 subcostal pain and tenderness, usually indicates the development of liver damage which is maximal 3–4 days after ingestion. In spite of a lack of significant early symptoms, patients who have taken an overdose of paracetamol should be transferred to 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 (see section 4.1).

Acetylcysteine protects the liver if given within 24 hours of ingesting paracetamol. Acetylcysteine, given intravenously, is most effective within 8 hours of overdosage 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 hospital, the need to continue antidote treatment can be assessed from plasma paracetamol concentration.

Opioid analgesic overdosage

Opioids cause coma, respiratory depression and pinpoint pupils. **Naloxone** is a specific antidote indicated if there is coma or bradypnoea. 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, are only partially reversed by naloxone.

Methadone has a very long duration of action and patients may need to be monitored for long periods after large overdoses.

Acute withdrawal syndromes may be precipitated by the use of naloxone in patients with a physical dependence on opioids or in overdosage 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 one 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 haemodialysis.

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 disease.

Methaemoglobinaemia

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

Cyanide poisoning

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

Acetylcysteine

Injection: 200 mg/ml in 10-ml ampoule.

Uses: paracetamol overdosage.

Precautions: asthma (see Adverse effects below, but do not delay treatment).

Dose:

Paracetamol overdosage, *by intravenous infusion*, **ADULT** and **CHILD**, initially 150 mg/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 litre 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 beta$_2$-agonist, such as salbutamol (see section 25.1).

Atropine

Injection: 1 mg (sulfate) in 1-ml ampoule.

Uses: organophosphate and carbamate poisoning; preoperative and intraoperative medication (section 1.3); mydriasis and cycloplegia (section 21.5).

Precautions: children, the 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 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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

Injection: 100 mg/ml in 10-ml ampoule.

See section 27.

Deferoxamine

Powder for injection: 500 mg (mesilate) in vial.

Uses: acute iron poisoning; chronic iron overload; aluminium overload.

Precautions: renal impairment (Appendix 4); eye and ear examinations are advised before and at 3-month intervals during treatment; aluminium encephalopathy (may exacerbate neurological dysfunction); pregnancy (Appendix 2) and breastfeeding (Appendix 3); 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 a 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 paraesthesia), Yersinia and mucormycosis infections, rash, renal impairment, and blood dyscrasias.

Dimercaprol

Injection in oil: 50 mg/ml in 2-ml ampoule.

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; see also Appendix 5).

Precautions: hypertension; renal impairment (discontinue or use with extreme caution if impairment develops during treatment; see also Appendix 4); any abnormal reaction such as hyperpyrexia should be assessed; the elderly; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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.

DL-methionine

Tablet: 250 mg.

Uses: paracetamol overdosage.

Precautions: severe liver disease (may precipitate hepatic encephalopathy); avoid concurrent use with activated charcoal.

Dose: Paracetamol overdosage, *by mouth*, **ADULT** and **CHILD** over 6 years, 2.5 g initially, followed by 3 further doses of 2.5 g every 4 hours, **CHILD** under 6 years, 1 g initially, followed by 3 further doses of 1 g every 4 hours.

Adverse effects: nausea, vomiting, drowsiness, irritability.

Methylthioninium chloride (methylene blue)

Injection: 10 mg/ml in 10-ml ampoule.

Uses: acute methaemoglobinaemia.

Contraindications: severe renal impairment; methaemoglobinaemia due to chlorate or induced by sodium nitrite in treatment of cyanide poisoning.

Precautions: G6PD deficiency (may cause haemolytic anaemia); monitor blood methaemoglobin throughout treatment; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Dose:

Acute methaemoglobinaemia, *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; haemolytic anaemia (in G6PD deficiency); methaemoglobinaemia (with high dosage); bluish skin discoloration; blue saliva, urine and faeces.

Naloxone

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

Uses: opioid overdosage; postoperative respiratory depression (section 25.2).

Precautions: physical dependence on opioids or other situations where acute withdrawal syndrome may be precipitated (see above); cardiovascular disease; pregnancy (Appendix 2).

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

Capsule or tablet: 250 mg.

Uses: poisoning by heavy metals, particularly lead and copper; Wilson disease; severe rheumatoid arthritis (section 2.4).

Contraindications: hypersensitivity; lupus erythematosus.

Precautions: monitor throughout treatment (including blood counts and urine tests); renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); avoid concurrent gold, chloroquine or immunosuppressive treatment; avoid oral iron within 2 hours of a dose; penicillin hypersensitivity (risk of cross-reactivity); **interactions**: Appendix 1.

BLOOD COUNTS. In Wilson disease, consider withdrawal if platelet count falls below 120 000/mm^3 or white blood cells fall below 2500/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 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 disease, *by mouth*, **ADULT,** 1.5–2 g daily in divided doses before food (maximum, 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 (minimum, 500 mg daily).

Adverse effects: initially nausea (less of a problem if taken with food and on retiring), anorexia, fever and skin reactions; taste loss (mineral supplements not recommended); blood disorders including thrombocytopenia, leukopenia, agranulocytosis, and aplastic anaemia; proteinuria, rarely haematuria (withdraw immediately); haemolytic anaemia, nephrotic syndrome, lupus erythematosus-like syndrome, myasthenia gravis-like syndrome, polymyositis (rarely with cardiac involvement), dermatomyositis, mouth ulcers, stomatitis, alopecia, bronchiolitis and pneumonitis, pemphigus, Goodpasture syndrome, and Stevens-Johnson syndrome also reported; male and female breast enlargement reported; in non-rheumatic conditions rheumatoid arthritis-like syndrome also reported; rash early in treatment (usually allergic – may need temporary withdrawal), late rash (reduce dose or withdraw treatment).

Potassium ferric hexacyanoferrate (II)$2H_20$ (Prussian blue)

Powder for oral administration.

Uses: thallium poisoning.

Contraindications: constipation; paralytic ileus.

Dose:

Treatment of thallium poisoning, *by duodenal tube*, **ADULT,** 125 mg/kg in 100 ml of mannitol, 15% twice daily (until urinary thallium stabilized at 500 micrograms/day or less).

Adverse effects: constipation, dark stools.

Sodium calcium edetate

Injection: 200 mg/ml in 5-ml ampoule.

Uses: lead poisoning.

Precautions: renal impairment (Appendix 4).

Dose:

Treatment of lead poisoning, *by intravenous infusion*, **ADULT** and **CHILD,** up to 40 mg/kg twice daily for up to 5 days; repeated if necessary after interval of 48 hours.

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: renal tubular necrosis; nausea, diarrhoea, abdominal cramps; pain at injection site, thrombophlebitis (if given too rapidly or as too concentrated a solution), fever, malaise, headache, myalgia, thirst, chills, histamine-like responses (sneezing, nasal congestion, lacrimation) and transient hypotension.

Sodium nitrite

Injection: 30 mg/ml in 10-ml ampoule.

Uses: cyanide poisoning (together with sodium thiosulfate).

Precautions: monitor plasma methaemoglobin levels; severe cardiovascular or cerebrovascular disease.

Dose:

Cyanide poisoning, *by slow intravenous injection* over 5–20 minutes, **ADULT,** 300 mg (followed by sodium thiosulfate); further dose of 150 mg after 30 minutes if symptoms recur; **CHILD,** 4–10 mg/kg (initially lower dose).

Adverse effects: vasodilatation resulting in syncope, hypotension, tachycardia, flushing, and headache; methaemoglobinaemia; cyanosis, dyspnoea, tachypnoea, nausea, vomiting, abdominal pain.

Sodium thiosulfate

Injection: 250 mg/ml in 50-ml ampoule.

Uses: cyanide poisoning (together with sodium nitrite); pityriasis versicolor (section 13.1)

Dose:

Cyanide poisoning, after administration of sodium nitrite, *by slow intravenous injection* over about 10 minutes, **ADULT,** 12.5 g; further dose of 6.25 g after 30 minutes if symptoms recur; **CHILD,** 400 mg/kg.

SECTION 5:
Anticonvulsants/antiepileptics

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 mainly 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, the size and the age of the patient. It should be increased gradually until an effective response is obtained. All antiepileptics 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 antiepileptic treatment. Patients should ideally remain under supervision throughout treatment.

Withdrawal

Treatment is normally continued for a minimum of two 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 antiepileptic 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 breastfeeding

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 two years; resumption of treatment may be considered after the first trimester. If antiepileptics 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 antiepileptics, particularly with **carbamazepine**, **valproic acid** and **phenytoin**. However, if there is good seizure control, there is probably no advantage in changing pregnant patients' antiepileptic 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 counselling and antenatal screening. To counteract the risk of neural tube defects, adequate folate supplements are advised for women before and during pregnancy (see section 10.1). In view of the risk of neonatal bleeding associated with **carbamazepine**, **phenobarbital,** and **phenytoin**, prophylactic phytomenadione (vitamin K_1) is recommended for the neonate and the mother before delivery (see section 10.2). Antiepileptic drugs can be continued during breastfeeding (see also Appendix 3).

Driving

Regulations are in place in many countries which may, for example, restrict driving by patients with epilepsy to those whose seizures are controlled. Furthermore, antiepileptic and anticonvulsant drugs may cause central nervous system depression, particularly in the early stages of treatment and patients affected by adverse effects such as drowsiness or dizziness should not operate machinery or drive.

Choice of antiepileptic 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 haematological 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 antiepileptic 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 antiepileptic drugs. Vigabatrin [not included on the 15th WHO Model List] or **valproic acid** (alone or in combination with clonazepam [not included on the 15th WHO Model List]) are used.

Febrile convulsions

Brief febrile convulsions usually respond to sponging with tepid water and by giving an antipyretic such as paracetamol (see section 2.1). 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 antiepileptics 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 which 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 hypoglycaemia; 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 [not included on the 15th WHO Model List] should be considered if alcohol abuse is suspected; pyridoxine should be administered if the status epilepticus is likely to be responsive to pyridoxine (see section 27).

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 [not included on the 15th WHO Model List] 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 anaesthesia 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.

Carbamazepine

Oral liquid: 100 mg/5 ml.
Tablet (chewable): 100 mg; 200 mg.
Tablet (scored): 100 mg; 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 5); renal impairment (Appendix 4); 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 note above; Appendix 2) and breastfeeding (see note above; Appendix 3); avoid sudden withdrawal (see note above); **interactions**: Appendix 1.

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 which is severe, progressive, and associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative antiepileptic).

SKILLED TASKS. May impair ability to perform skilled tasks, for example, operating machinery or driving; see also note 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/litre (17–50 micromol/litre).

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, diarrhoea or constipation; commonly, mild transient generalized erythematous rash (withdraw if rash worsens or is accompanied by other symptoms); leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis, and aplastic anaemia); cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, and disturbances of bone metabolism with osteomalacia also reported; confusion and agitation in the elderly.

Diazepam

Injection: 5 mg/ml in 2-ml ampoule (intravenous or rectal).

Drug subject to international control under the Convention on Psychotropic Substances (1971).

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

Uses: 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 (section 1.3); anxiety disorders (section 24.3).

Contraindications: respiratory depression; acute pulmonary insufficiency; sleep apnoea; 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 (see note above; Appendix 2) and breastfeeding (see note above; Appendix 3); reduce dose in the elderly or debilitated patients and in hepatic impairment (avoid if severe; Appendix 5); renal impairment (Appendix 4); avoid prolonged use and abrupt withdrawal; when given intravenously facilities for reversing respiratory depression with mechanical ventilation must be at hand (see note below); porphyria; **interactions**: Appendix 1.

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 centre with intensive care facilities. Prolonged intravenous infusion may lead to accumulation and delay recovery.

SKILLED TASKS. May impair ability to perform skilled tasks, for example, operating machinery or driving; see also note above.

Dose:

Status epilepticus, emergency management of recurrent epileptic seizures, *by slow intravenous injection* (at a rate of 5 mg/minute), **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 1 mg per year of age);

by rectum as solution, **ADULT** and **CHILD** over 10 kg, 500 micrograms/kg; **ELDERLY,** 250 micrograms/kg; repeated if necessary every 12 hours; if convulsions not controlled, other measures should be instituted.

Febrile convulsions (preferred treatment), *by rectum* (as a *solution*) [injection solution may be used], **CHILD** over 10 kg, 500 micrograms/kg (maximum, 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/minute), **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/minute), **ADULT,** 10–20 mg.

Adverse effects: drowsiness and lightheadedness 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 apnoea, pain and thrombophlebitis (with injection).

Ethosuximide

Capsule: 250 mg.

Oral liquid: 250 mg/5 ml.

Ethosuximide is a complementary antiepileptic medicine.

Uses: absence seizures.

Precautions: hepatic or renal impairment (blood counts and hepatic and renal function tests recommended); pregnancy (see note above; Appendix 2) and breastfeeding (see note above; Appendix 3); avoid sudden withdrawal (see note above); porphyria; **interactions**: Appendix 1.

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 note 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 1 g and above should be taken as 2 or more divided doses.

NOTE. Plasma concentration for optimum response, 40–100 mg/litre (300–700 micromol/litre).

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 haematological disorders (including leukopenia, agranulocytosis, aplastic anaemia, 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

Injection: 500 mg/ml in 2-ml ampoule; 500 mg/ml in 10-ml ampoule.

Uses: prevention of recurrent seizures in eclampsia; prevention of seizures in pre-eclampsia.

Precautions: see note above; myasthenia gravis; hepatic impairment (Appendix 5); renal impairment (Appendix 4); pregnancy (Appendix 2); **interactions**: Appendix 1.

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 hypermagnesaemia (see also notes above), including nausea, vomiting, thirst, flushing of skin,

hypotension, arrhythmias, coma, respiratory depression, drowsiness, confusion, loss of tendon reflexes, and muscle weakness.

Phenobarbital

Injection: 200 mg/ml (phenobarbital sodium).
Oral liquid: 15 mg/5 ml (phenobarbital) or 5 ml (phenobarbital sodium).
Tablet: 15–100 mg (phenobarbital).

Drug subject to international control under the Convention on Psychotropic Substances (1971).

Uses: generalized tonic–clonic seizures; partial seizures; neonatal seizures; febrile convulsions; status epilepticus (see note above).

Contraindications: porphyria; absence seizures.

Precautions: the elderly, debilitated, children (may cause behavioural changes); impaired renal function (Appendix 4); impaired hepatic function (Appendix 5), respiratory depression (avoid if severe); pregnancy (see note above; Appendix 2) and breastfeeding (see note above; Appendix 3); avoid sudden withdrawal (see note above); **interactions**: Appendix 1.

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery or driving; see also notes 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 in 10 with water for injections), **NEONATE,** 5–10 mg/kg every 20–30 minutes up to plasma concentration of 40 mg/litre.

Status epilepticus, *by intravenous injection* (dilute injection 1 in 10 with water for injection), **ADULT,** 10 mg/kg at a rate of not more than 100 mg/minute (up to a maximum total dose of 1 g); **CHILD,** 5–10 mg/kg at a rate of not more than 30 mg/minute.

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

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 anaemia (may be treated with folic acid); osteomalacia; status epilepticus (on treatment withdrawal); hypotension, shock, laryngospasm and apnoea (with intravenous injection).

Phenytoin

Capsule: 25 mg; 50 mg; 100 mg (sodium salt).
Injection: 50 mg/ml in 5-ml vial (sodium salt).
Oral liquid: 25–30 mg/5 ml.
Tablet: 25 mg; 50 mg; 100 mg (sodium salt).
Tablet (chewable): 50 mg.

NOTE. The presence of both the 25 mg/5 ml and the 30 mg/5 ml strengths of the oral liquid on the same market should be avoided to prevent confusion in prescribing and dispensing.

Uses: generalized tonic–clonic seizures; partial seizures; status epilepticus.

Contraindications: porphyria; avoid parenteral use in sinus bradycardia, sino-atrial block, second- and third-degree heart block, Stokes-Adams syndrome.

Precautions: hepatic impairment (reduce dose; Appendix 5); pregnancy (increased risk of birth defects and neonatal bleeding, see note above; Appendix 2) and breastfeeding (see note above; Appendix 3); diabetes mellitus; monitor blood counts; hypotension and heart failure (especially with parenteral use); in case of intravenous administration, resuscitation facilities must be available and the injection solution alkaline (irritant to tissues); **interactions**: Appendix 1.

BLOOD OR SKIN DISORDERS. Patients or their carers should be told how to recognize signs of blood or skin disorders and advised to seek immediate medical attention if symptoms such as sore throat, rash, mouth ulcers, bruising, or bleeding develop. Leukopenia which is severe, progressive or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative antiepileptic).

SKILLED TASKS. May impair ability to perform skilled tasks, for example, operating machinery or driving; see also note above.

Dose:

Generalized tonic–clonic seizures, partial seizures, *by mouth*, **ADULT,** initially 3–4 mg/kg daily (as a single dose or in 2 divided doses), increased gradually at intervals of 2 weeks as necessary (with plasma phenytoin concentration monitoring); to a usual maintenance dose of 200–500 mg daily; **CHILD,** initially 3–5 mg/kg daily in 2 divided doses, increased gradually according to clinical response and plasma phenytoin concentration, to a usual maintenance dose of 4–8 mg/kg daily (maximum, 300 mg daily).

NOTE. Plasma concentration for optimum response 10–20 mg/litre (40–80 micromol/litre).

PATIENT ADVICE. Preferably taken with or after food.

Status epilepticus,

by slow intravenous injection or *by intravenous infusion* (with blood pressure and ECG monitoring), **ADULT,** 15 mg/kg at a rate of not more than 50 mg/minute, as a loading dose; maintenance doses of about 100 mg;

by mouth or *by slow intravenous injection* should be given thereafter at intervals of 6–8 hours, with monitoring of plasma concentrations; rates and dose reduced according to weight; **CHILD,** 15 mg/kg as a loading dose at rate of 1 mg/kg/minute (not exceeding 50 mg/minute); **NEONATE,** 15–20 mg/kg as a loading dose at rate of 1–3 mg/kg/minute.

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: gastric intolerance, headache, sleeplessness, agitation (during initial phase); sedation, confusion, blurred vision, ataxia, nystagmus, diplopia, slurred speech, cerebellar-vestibular symptoms, behavioural disorders, hallucinations, hyperglycaemia (may be signs of overdosage); gingival hyperplasia, acne, coarse facies, hirsutism, fever, hepatitis, neurological changes including peripheral neuropathy, choreiform movements, impaired cognition, and increased seizure frequency; osteomalacia, rickets (associated with reduced plasma calcium levels); lymph-node enlargement; vertigo; rash (discontinue; if mild re-introduce cautiously, but discontinue if recurrence); very rarely Stevens-Johnson syndrome (erythema multiforme), systemic lupus erythematosus, and toxic epidermal necrolysis; rarely blood disorders including megaloblastic anaemia (may be treated with folic acid), leukopenia, thrombocytopenia, and agranulocytosis with or without bone marrow depression; with intravenous administration, cardiovascular and central nervous system depression (particularly if administered too rapidly) with arrhythmias, hypotension and cardiovascular collapse, and alterations in respiratory function (including respiratory collapse).

Valproic acid

Oral liquid: 200 mg/5 ml.
Tablet (crushable): 100 mg.
Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate).

Uses: all forms of epilepsy; 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 5); ensure no undue potential for bleeding before starting, and also before major surgery or anticoagulant therapy; renal impairment (Appendix 4); pregnancy (increased risk of birth defects and neonatal

bleeding, see note above; Appendix 2); breastfeeding (see note above; Appendix 3); systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal (see note above); **interactions**: Appendix 1.

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, oedema, vomiting, abdominal pain, drowsiness, jaundice, or spontaneous bruising or bleeding develop.

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 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 haematological parameters); **CHILD** under 12 years, over 20 kg, initially 400 mg daily in divided doses, increased until control (usually in range of 20–30 mg/kg daily); maximum, 35 mg/kg daily.

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

Adverse effects: gastrointestinal irritation, nausea, increased appetite, and weight gain, hyperammonaemia; ataxia, tremor; transient hair loss (regrowth may be curly); oedema, thrombocytopenia, inhibition of platelet aggregation; impaired hepatic function and rarely fatal hepatic failure (withdraw treatment immediately if malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, drowsiness, or loss of seizure control; see also note in Precautions); sedation reported and also increased alertness; behavioural 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, amenorrhoea, gynaecomastia, hearing loss, Fanconi syndrome, dementia, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme), vasculitis, hirsutism, and acne reported.

SECTION 6:
Anti-infective medicines

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6.1 Anthelminthics

6.1.1 Intestinal anthelminthics

Cestode infections

Cestode infections (tapeworms) include intestinal taeniasis and cysticercosis, hymenolepiasis (dwarf tapeworm), diphyllobothriasis, 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 tumour-like infiltration (alveolar echinococcosis) in the liver, lungs, or other organs.

Diphyllobothriasis

In diphyllobothriasis, **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–reaspiration") 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.

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 to 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 it can therefore be used to treat neurocysticercosis. However, because dying and disintegrating cysts may

induce localized cerebral oedema, treatment with praziquantel must always be undertaken in a hospital setting. In addition, a corticosteroid is usually given to reduce the inflammatory response. **Albendazole** also kills neurocysticerci when given daily for one month; a corticosteroid or an antihistamine is also given to reduce any inflammatory reaction. Surgery may be the preferred treatment for neurocysticerosis in some cases. The longer-established **niclosamide** acts only against the adult intestinal worms.

Cestode infections due to *T. solium* occurring during pregnancy should always be treated immediately (with praziquantel or niclosamide, but not with albendazole) because of the risk of cysticercosis.

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 anthelminthics, **albendazole** or **mebendazole,** are also effective.

Capillariasis

Capillariasis is caused by infection of the intestine with *Capillaria philippinensis*. Prolonged treatment with **albendazole** or **mebendazole** offers the only prospect of cure.

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 one further dose should be given 2–4 weeks later. Piperazine [not included on the 15th WHO Model List] 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 anaemia 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-trimester of pregnancy, children, and debilitated patients. In hookworm, broad-spectrum anthelminthics 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 drugs are contraindicated for the treatment of cestode infections in pregnancy (see Cestode infections above).

Levamisole is effective in the treatment of mixed roundworm and hookworm infections. **Pyrantel** has been highly effective against hookworm in some community-based control programmes, although several doses are often needed to eliminate *Necator americanus* infection. Patients with iron-deficiency anaemia 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 haemoglobin concentration of 12 g/100 ml is attained (see also section 10.1).

Strongyloidiasis

Strongyloidiasis is an infection of the small intestine caused by *Strongyloides stercoralis*. All infected patients should be treated. Ivermectin (section 6.1.2) in a single dose of 200 micrograms/kg or 200 micrograms/kg/day on 2 consecutive days is the treatment of choice for chronic strongyloidiasis but it may not be available in all countries. **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 the 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 faecal 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.

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).

Tissue nematode infections

Tissue nematode infections include angiostrongyliasis, anisakiasis, cutaneous larva migrans, dracunculiasis, trichinellosis, and visceral larva migrans.

Angiostrongyliasis

Angiostrongyliasis is caused by infection with the larvae of the rat lungworm, *Parastrongylus cantonensis* (*Angiostrongylus cantonensis*). Symptomatic treatment pending spontaneous recovery is often all that is required.

Anisakiasis

Anisakiasis is caused by infection with seafood containing larvae of *Anisakis*, *Contracaecum*, or *Pseudoterranova* spp. In anisakiasis, anthelminthic treatment is rarely necessary. Prevention is dependent upon informing communities of the hazards of eating raw or inadequately prepared saltwater fish; early evisceration of fish after capture, and freezing of seafood at -20°C for at least 60 hours before sale.

Cutaneous larva migrans

Cutaneous larva migrans (creeping eruption) is caused by infection with larvae of animal hookworms, usually *Ancylostoma braziliense* and *A. caninum* which infect cats and dogs. **Albendazole** in a single dose of 400 mg is effective.

Dracunculiasis

Dracunculiasis (dracontiasis, guinea-worm infection) is caused by infection with *Dracunculus medinensis,* acquired through drinking water containing larvae that develop in small freshwater crustaceans. Metronidazole (section 6.5.1) (25 mg/kg daily for 10 days, up to a daily maximum of 750 mg for children) provides rapid symptomatic relief. It also weakens the anchorage of the worms in the subcutaneous tissues, and they can then be removed by traction. However, since it has no effect on the larvae of pre-emergent worms, it does not immediately prevent transmission.

Trichinellosis

Trichinellosis (trichinosis) is caused by infection with the larvae of *Trichinella spiralis*. Each case of confirmed or even suspected trichinellosis infection should be treated in order to prevent the continued production of larvae. In

both adults and children, **mebendazole** (200 mg daily for 5 days), **albendazole** (400 mg daily for 3 days), and **pyrantel** (10 mg/kg daily for 5 days) are all effective. Prednisolone (40–60 mg daily) may be needed to alleviate the allergic and inflammatory symptoms (see also section 3).

Visceral larva migrans

Visceral larva migrans (toxocariasis) is caused by infection with the larval forms of *Toxocara canis* and less commonly, *T. cati* (which infect dogs and cats). Treatment should be reserved for symptomatic infections. A 3-week oral course of diethylcarbamazine (section 6.1.2) kills the larvae and arrests the disease, but established lesions are irreversible. To reduce the intensity of allergic reactions induced by dying larvae, dosage is commonly commenced at 1 mg/kg twice daily and raised progressively to 3 mg/kg twice daily (adults and children).

Ocular larva migrans occurs when larvae invade the eye, causing a granuloma which may result in blindness. In order to suppress allergic inflammatory responses in patients with ophthalmic lesions, prednisolone should be administered concurrently, either topically or systemically.

Albendazole

Tablet (chewable): 400 mg.

Uses: *Echinococcus multilocularis* and *E. granulosus* infections prior to surgery or not amenable to surgery; neurocysticercosis; nematode infections including ascariasis, capillariasis, enterobiasis, hookworm infections, strongyloidiasis, trichostrongyliasis, trichuriasis; filariasis (section 6.1.2).

Contraindications: pregnancy (see introductory note above and Precautions; Appendix 2).

Precautions: liver function tests and blood counts recommended before longer-term treatment and twice during each cycle; exclude pregnancy before starting treatment (advise patients to use non-hormonal contraception during and for 1 month after treatment); breastfeeding (Appendix 3); **interactions**: Appendix 1.

Dose:

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.

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.

Capillariasis, by mouth, **ADULT** and **CHILD** over 2 years, 400 mg daily for 10 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.

Levamisole

Tablet: 50 mg; 150 mg (as hydrochloride).

Uses: ascariasis, hookworm infections, and mixed ascariasis with hookworm infections.

Contraindications: breastfeeding (Appendix 3).

Precautions: pregnancy (Appendix 2); **interactions**: Appendix 1.

Dose:

Ascariasis, hookworm infections, and mixed ascariasis with hookworm infections, *by mouth*, **ADULT** and **CHILD,** 2.5 mg/kg as a single dose; in severe hookworm infection, a second dose may be given after 7 days.

Adverse effects: abdominal pain, nausea, vomiting, dizziness, headache.

Mebendazole

Tablet (chewable): 100 mg; 500 mg.

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

Uses: *Echinococcus granulosus* and *E. multilocularis* infections prior to surgery or not amenable to surgery; nematode infections including ascariasis, capillariasis, enterobiasis, hookworm infections, and trichuriasis.

Contraindications: pregnancy (see also introductory note above; Appendix 2).

Precautions: blood counts and liver function tests recommended with high-dose regimens; breastfeeding (Appendix 3); **interactions**: Appendix 1.

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 faeces, second course after 3–4 weeks; alternatively (especially for mass treatment control programmes), 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.

Capillariasis, by mouth, **ADULT** and **CHILD** over 2 years, 200 mg daily for 20–30 days; for mass treatment control programmes, by mouth, **ADULT** and **CHILD** over 2 years, 500 mg as a single dose 4 times a year.

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

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 antiemetic before treatment; not effective against larval worms; pregnancy (Appendix 2).

Dose:

T. solium infection, *by mouth*, **ADULT** and **CHILD** over 6 years, 2 g as a single dose after a light breakfast, followed after 2 hours by a laxative; **CHILD** under 2 years, 500 mg, 2–6 years, 1 g.

T. saginata and *Diphyllobothrium latum* infections, *by mouth,* as for *T. solium* but half the dose may be taken after breakfast and the remainder 1 hour later followed by a laxative after 2 hours.

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; lightheadedness; pruritus.

Praziquantel

Tablet: 150 mg; 600 mg.

Uses: cestode *(Taenia saginata*, *T. solium*, *Hymenolepis nana* and *Diphyllobothrium latum)* infections; schistosomiasis and other trematode infections (section 6.1.3).

Contraindications: ocular cysticercosis.

Precautions: neurocysticercosis (requires corticosteroid cover with monitoring in a hospital setting); pregnancy (Appendix 2) and breastfeeding (avoid during, and for 72 hours, after treatment, Appendix 3); **interactions**: Appendix 1.

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery or driving.

Dose:

Taenia saginata and *T. solium* infections, *by mouth*, **ADULT** and **CHILD** over 4 years, 5–10 mg/kg as a single dose.

Hymenolepis nana infection, *by mouth*, **ADULT** and **CHILD** over 4 years, 15–25 mg/kg as a single dose.

*Diphyllobothrium latum i*nfection, *by mouth*, **ADULT** and **CHILD** over 4 years, 10–25 mg/kg as a single dose.

Cysticercosis, *by mouth*, **ADULT** and **CHILD** over 4 years, 50 mg/kg daily in 3 divided doses for 14 days with prednisolone (or similar corticosteroid) given 2–3 days before and throughout treatment period.

Dermal cysticercosis, *by mouth*, **ADULT** and **CHILD** over 4 years, 60 mg/kg daily in 3 divided doses for 6 days.

Adverse effects: abdominal discomfort, nausea, vomiting, diarrhoea, malaise; headache, dizziness, drowsiness; rarely hypersensitivity reactions including fever, urticaria, pruritus, and eosinophilia (may be due to dead and dying parasites); in neurocysticercosis, headache, hyperthermia, seizures, and intracranial hypertension (inflammatory response to dead and dying parasites in the central nervous system).

Pyrantel

Oral liquid: 50 mg (as embonate)/ml.
Tablet (chewable): 250 mg (as embonate).

Uses: nematode infections, including ascariasis, hookworm infections, enterobiasis, trichostrongyliasis and trichinellosis.

Precautions: pregnancy (Appendix 2); breastfeeding (Appendix 3); liver disease (reduce dose).

Dose:

Ascariasis, trichostrongyliasis, *by mouth*, **ADULT** and **CHILD,** 10 mg/kg as a single dose.

Hookworm infections, *by mouth*, **ADULT** and **CHILD,** 10 mg/kg as a single dose; in severe infections, 10 mg/kg daily for 4 days.

Enterobiasis, *by mouth*, **ADULT** and **CHILD,** 10 mg/kg as a single dose with a second dose after 2–4 weeks.

Adverse effects: mild gastrointestinal disturbances, headache, dizziness, drowsiness, insomnia, rash, and elevated liver enzymes.

6.1.2 Antifilarials

Loiasis

Loiasis is an infection with the filarial nematode, *Loa loa,* and is transmitted by the biting tabanid fly, *Chrysops*. **Diethylcarbamazine** is effective against both adult worms and larvae; a single weekly dose is normally effective as prophylaxis. During individual treatment, particularly of persons with heavy microfilaraemia (>50 000 microfilariae/ml blood), a condition simulating meningoencephalitis occasionally occurs. This probably results from sludging of moribund microfilariae within cerebral capillaries. The frequency of meningoencephalitis associated with diethylcarbamazine therapy of loiasis is

reported to be 1.25%, with a mortality rate of about 50% in affected patients; treatment with diethylcarbamazine should be stopped at the first sign of cerebral involvement (and specialist advice sought). Permanent cerebral damage is common among patients who survive and this possibility should be considered when deciding on treatment. Treatment of heavily infected patients should thus begin at low dosages and corticosteroid and antihistamine cover should be provided for the first 2–3 days.

Lymphatic filariasis

Lymphatic filariasis is caused by infection with *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi,* or *B. timori* (brugian filariasis). Occult filariasis (tropical pulmonary eosinophilia) is a clinical variant of *W. bancrofti* infection. Individual treatment with **diethylcarbamazine**, which has both microfilaricidal and macrofilaricidal activity, is effective. Total cumulative dosages of 72 mg/kg are generally recommended for *W. bancrofti* infections; half this dose is usually effective in *B.malayi* and *B. timori* infections. In all cases, treatment is best initiated with smaller doses for 2–3 days to avoid the danger of immunological reactions. Rigorous hygiene to the affected limbs with adjunctive measures to minimize infection and promote lymph flow are important for reducing acute episodes of inflammation.

In communities where filariasis is endemic, annual administration of single doses of **albendazole** (400 mg) with either **diethylcarbamazine** (6 mg/kg) or **ivermectin** (200 micrograms/kg) is effective for interrupting transmission; this treatment should be continued for at least 5 years. Trials in India and China have shown that the consistent use over a period of 6–12 months of table salt containing diethylcarbamazine, 0.1%, can eliminate *W. bancrofti*; a concentration of 0.3% for 3–4 months may be required where *B. malayi* is endemic.

Onchocerciasis

Onchocerciasis (river blindness) is caused by infection with the filarial nematode, *Onchocerca volvulus*. The vector is the blackfly which breeds near fast-flowing rivers. **Ivermectin** has transformed suppressive treatment of onchocerciasis and is now used extensively in control programmes in many countries. It rapidly eliminates microfilariae from the skin and more gradually from the eye. Its microfilaricidal action is more persistent than that of diethylcarbamazine; it is also less liable to provoke adverse reactions. A single oral dose of ivermectin reduces the microfilarial count to low levels for up to a year. It appears both to kill microfilariae and to inhibit their expulsion from the uterus of female worms. A single annual dose may suppress microfilaraemia to a degree that prevents development of clinical disease. Although the drug is generally well tolerated, it is advisable to provide medical

support as part of treatment programmes. Patients with a heavy microfilarial load occasionally react adversely; very rarely, transient severe postural hypotension has occurred within 12–24 hours of treatment.

Treatment of pregnant women with ivermectin should be limited to those situations where the risk of complications from untreated onchocerciasis exceeds the potential risk to the fetus from treatment. Mass treatment programmes should not include children under 15 kg, pregnant patients or those with severe illness.

Diethylcarbamazine has been now largely superseded by ivermectin as a microfilaricide in onchocerciasis because of the frequency with which it induces severe host (Mazzotti) reactions which are characterized by itching, rash, oedema, pain and swelling of the lymph nodes, fever, and severe eye lesions.

Suramin sodium is the only macrofilaricide that is currently available for use against *Onchocerca volvulus*. Administered intravenously over a period of several weeks suramin also kills microfilariae. It is, however, one of the most toxic substances used in clinical medicine and should always be given under medical supervision in a hospital. A careful assessment must always be made of the patient's capacity to withstand the effects of suramin treatment both before and during administration.

Diethylcarbamazine

Tablet: 50 mg; 100 mg (dihydrogen citrate).

Diethylcarbamazine is a complementary antifilarial medicine.

Uses: systemic lymphatic filariasis and occult filariasis; loiasis; tissue nematode infections, in particular, visceral larva migrans (section 6.1.1).

Contraindications: pregnancy (delay treatment until after delivery, Appendix 2).

Precautions: renal impairment (reduce dose; Appendix 4); cardiac disorders; other severe acute disease (delay diethylcarbamazine treatment until after recovery).

Dose:

Lymphatic filariasis (bancroftian), *by mouth*, **ADULT** and **CHILD** over 10 years, 1 mg/kg as a single dose on the first day, increased gradually over 3 days to 6 mg/kg daily, preferably in divided doses after meals, for 12 days; **CHILD** under 10 years, half the adult dose; mass treatment control programmes, **ADULT** and **CHILD** over 10 years, 6 mg/kg in divided doses over 24 hours, once a year; child under 10 years, half the adult dose.

Lymphatic filariasis (brugian), *by mouth*, **ADULT** and **CHILD** over 10 years, 1 mg/kg as a single dose on the first day, increased gradually over 3 days to

3–6 mg/kg daily, preferably in divided doses after meals, for 6–12 days; **CHILD** under 10 years, half the adult dose; mass treatment control programmes, **ADULT** and **CHILD** over 10 years, 3–6 mg/kg in divided doses over 24 hours, 6 times at weekly or monthly intervals; **CHILD** under 10 years, half the adult dose.

Occult filariasis, *by mouth*, **ADULT,** 8 mg/kg daily for 14 days, repeated as necessary if symptoms return.

NOTE. The above dose regimens are intended only as a guide, since many countries have developed specific treatment regimens.

Loiasis, treatment, by mouth, **ADULT,** 1 mg/kg as a single dose on the first day, doubled on two successive days, then adjusted to 2–3 mg/kg 3 times daily for a further 18 days

Loiasis, prophylaxis, by mouth, **ADULT**, 300 mg weekly for as long as exposure occurs

PATIENT ADVICE. Complete the prescribed course as directed to minimize allergic reactions to dying parasites.

Adverse effects: headache, dizziness, drowsiness, nausea and vomiting; immunological reactions within a few hours of the first dose, subsiding by fifth day of treatment, including fever, headache, joint pain, dizziness, anorexia, malaise, transient haematuria, urticaria, vomiting, and asthma in asthmatics (similar to the Mazzotti reaction) induced by disintegrating microfilariae; nodules formed by recently killed worms (palpable subcutaneously and along the spermatic cord); transient lymphangitis and exacerbation of lymphoedema.

Ivermectin

Tablet (scored): 3 mg; 6 mg.

Uses: suppressive treatment of onchocerciasis; filariasis; strongyloidiasis (section 6.1.1); hyperkeratotic scabies (section 13.6).

Contraindications: pregnancy (delay treatment until after delivery, Appendix 2).

Precautions: breastfeeding (avoid treating mother until infant is 1 week old, Appendix 3).

Dose:

Suppression of microfilariae, *by mouth*, **ADULT** and **CHILD** over 5 years (and weighing over 15 kg), 150 micrograms/kg as a single dose once a year

PATIENT ADVICE. Avoid food or alcohol for at least 2 hours before and after a dose.

Adverse effects: mild ocular irritation; somnolence; raised liver enzymes; rarely postural hypotension; mild Mazzotti reaction within 3 days of treatment, resulting from death of microfilariae, including fever, headache, sore throat,

cough, pruritus, rash, conjunctivitis, arthralgia, myalgia, lymphadenopathy, lymphadenitis, oedema, weakness, tachycardia, nausea and vomiting, and diarrhoea.

Suramin sodium

Powder for injection: 1 g in vial.

Suramin sodium is a complementary antifilarial medicine.

Uses: curative treatment of onchocerciasis; trypanosomiasis (section 6.5.5.1).

Contraindications: previous anaphylaxis or suramin sensitivity; pregnancy (delay treatment until after delivery); severe liver or renal function impairment; the elderly or debilitated; total blindness (unless required for relief from intensely itchy lesions).

Precautions: administer only under close medical supervision in hospital and with general condition of patient improved as far as possible before treatment (see introductory note above); first dose (possible loss of consciousness; see under Dose below); maintain satisfactory food and fluid intake during treatment; urine tests before and weekly during treatment recommended (reduce dose if moderate albuminuria, discontinue immediately if severe albuminuria or casts in urine).

Dose:

Curative treatment of onchocerciasis, *by slow intravenous injection*, **ADULT,** initially 3.3 mg/kg as a single dose (see note below), followed at weekly intervals by incremental doses of 6.7 mg/kg, 10.0 mg/kg, 13.3 mg/kg, 16.7 mg/kg, and 16.7 mg/kg on weeks 2 to 6, respectively (total dose, 66.7 mg/kg over 6 weeks).

RECONSTITUTION OF INJECTION. Reconstitute in water for injections to produce a final concentration of 10%.

FIRST (TEST) DOSE. Administer first dose with particular caution; wait at least 1 minute after injecting the first few microlitres; inject the next 0.5 ml over 30 seconds and wait 1 minute; inject the remainder over several minutes.

Adverse effects: rarely immediate and potentially fatal reaction with nausea, vomiting, shock, and loss of consciousness during first dose (see note above); albuminuria; abdominal pain; severe diarrhoea; stomal ulceration; exfoliative dermatitis; fever; tiredness; anorexia; malaise; polyuria; thirst; raised liver enzyme values; paraesthesia and hyperaesthesia of palms and soles; swelling, tenderness and abscess formation around adult worms; urtico-papular rash, painful hip, hand and foot joints, inflammatory and degenerative changes in optic nerve and retina (due to dying microfilariae).

6.1.3 Antischistosomals and antitrematode medicine

Fluke infections

The intestinal flukes include *Fasciolopsis buski*, *Metagonimus yokogawai*, *Heterophyes heterophyes*, *Echinostoma* spp. and *Gastrodiscoides hominis*. The liver flukes include *Clonorchis sinensis*, *Opisthorchis viverrini*, *O. felineus* and *Fasciola hepatica*. In some areas *C. sinensis* and *Opisthorchis* spp. infections are strongly associated with cholangiocarcinoma (cancer of the bile ducts). The lung flukes are of the genus *Paragonimus*.

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.

Triclabendazole, a benzimidazole compound is highly effective and well tolerated, as a single dose or two divided doses, for both *Fasciola* and *Paragonimus* infections.

Schistosomiasis

Schistosomiasis, a waterborne parasitic infection, is caused by several species of trematode worms (blood flukes). Its socioeconomic impact as a parasitic disease is outstripped only by that of malaria. Intestinal schistosomiasis is caused principally by *Schistosoma mansoni* as well as *S. japonicum*, *S. mekongi*, and *S. intercalatum*. Urinary schistosomiasis is caused by *S. haematobium*. The latter is an important predisposing cause of squamous cell cancer of the bladder.

Praziquantel has transformed the treatment of schistosomiasis and is often effective in a single dose, against all species of the parasite. It can be of particular value in patients with mixed infections and those who do not respond adequately to other drugs. It is also extremely well tolerated and well suited for mass treatment control programmes. Extensive use over several years has provided no evidence of serious adverse effects or long-term toxicity, nor has mutagenic or carcinogenic activity been shown in experimental animals.

Other drugs still widely used in the treatment of schistosomiasis include **oxamniquine**, which is effective against *S. mansoni*. Strains resistant to oxamniquine, which have been reported in South America, have been effectively treated with praziquantel. It is preferable to delay treatment with oxamniquine in pregnant women until after delivery unless immediate intervention is essential. Due to the lack of information on whether oxamniquine is excreted in breast milk, it is preferable not to administer it to nursing mothers.

Oxamniquine

Capsule: 250 mg.

Oral liquid: 250 mg/5 ml.

Oxamniquine is a complementary antischistosomal medicine.

Uses: intestinal schistosomiasis due to *Schistosoma mansoni* (acute stage and chronic hepatosplenic disease).

Precautions: epilepsy (close observation required as treatment may precipitate seizures); pregnancy (see introductory note above; Appendix 2) and breastfeeding (see introductory note above; Appendix 3).

SKILLED TASKS. May impair ability to perform skilled tasks, for example, operating machinery or driving.

Dose:

Intestinal schistosomiasis due to *S. mansoni* (west Africa, South America, Caribbean islands), *by mouth*, **ADULT,** 15 mg/kg as a single dose; **CHILD** under 30 kg, 20 mg/kg in 2 divided doses.

Intestinal schistosomiasis due to *S. mansoni* (east and central Africa, Arabian peninsula), *by mouth*, **ADULT** and **CHILD,** 30 mg/kg in 2 divided doses

Intestinal schistosomiasis due to *S. mansoni* (Egypt and southern Africa), **ADULT** and **CHILD,** 60 mg/kg in divided doses over 2–3 days (maximum, single dose 20 mg/kg).

Adverse effects: commonly, dizziness and drowsiness; headache, nausea, vomiting, diarrhoea; intense reddish discoloration of urine; rarely, urticaria, hallucinations, and epileptiform convulsions; raised liver enzyme values; transient fever, eosinophilia, and scattered pulmonary infiltrates (Loeffler syndrome) reported after 3-day course in patients in Egypt and eastern Mediterranean.

Praziquantel

Tablet: 600 mg.

Uses: intestinal schistosomiasis; urinary schistosomiasis; intestinal, liver, and lung; fluke infections; cestode infections (section 6.1.1).

Contraindications: ocular cysticercosis (see section 6.1.1).

Precautions: *Paragonimus* infections — treatment in hospital as may be central nervous system involvement; pregnancy (unless immediate treatment required, delay treatment until after delivery; Appendix 2); breastfeeding (avoid during and for 72 hours after treatment); pregnancy (Appendix 2) and breastfeeding (Appendix 3); areas endemic for cysticercosis (possible oedematous reaction); **interactions**: Appendix 1.

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery or driving.

Dose:

Intestinal fluke infections, by mouth, **ADULT** and **CHILD** over 4 years, 25 mg/kg as a single dose.

Liver and lung fluke infections, by mouth, **ADULT** and **CHILD** over 4 years, 25 mg/kg 3 times daily for 2 consecutive days; alternatively 40 mg/kg as a single dose; treatment may need to be extended for several days in paragonimiasis.

Schistosomiasis, *by mouth*, **ADULT** and **CHILD** over 4 years, 40–60 mg/kg as a single dose; or in 3 divided doses of 20 mg/kg at intervals of 4–6 hours.

Adverse effects: abdominal discomfort, nausea, vomiting, malaise, headache, dizziness, drowsiness, rectal bleeding; rarely hypersensitivity reactions, including fever, pruritus, and eosinophilia (may be due to dead and dying parasites).

Triclabendazole

Tablet: 250 mg.

Uses: fascioliasis; paragonimiasis.

Precautions: *Paragonimus* infections (treatment in hospital recommended due to possible central nervous system involvement); severe fascioliasis (biliary colic due to obstruction by dying worms).

Dose:

Fascioliasis, *by mouth*, **ADULT** and **CHILD** over 4 years, 10 mg/kg as a single dose.

Paragonimiasis, *by mouth*, **ADULT** and **CHILD** over 4 years, 20 mg/kg in 2 divided doses.

Adverse effects: gastrointestinal discomfort; headache.

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).

Antibacterial policy

Local policies often limit the availability of antibacterials in order to achieve reasonable economy consistent with adequate cover, and to reduce the development of resistant organisms. A policy may allow a range of drugs for general use and permit use of other drugs only on the advice of a microbiologist or physician responsible for the control of infectious diseases.

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 (e.g. 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.

Superinfection

In general, broad-spectrum antibacterial drugs such as the cefalosporins are more likely to be associated with adverse reactions related to the selection of resistant organisms, for example, fungal infections or antibiotic-associated colitis (pseudomembranous colitis); other problems associated with superinfection include vaginitis and pruritus ani.

6.2.1 Beta Lactam medicines

Beta Lactam antibiotics, which include penicillins, cefalosporins, and carbapenems, share a common structure; they are bactericidal, their mechanism of action resulting from inhibition of peptidoglycan, a mucopeptide in bacterial cell walls. **Benzylpenicillin** and **phenoxymethylpenicillin** are active against susceptible strains of Gram-positive bacteria and Gram-negative bacteria, spirochaetes, and actinomycetes, but are inactivated by penicillinase and other Beta Lactamases. **Benzathine benzylpenicillin** and **procaine benzylpenicillin** are long-acting preparations which slowly release benzylpenicillin 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 isoxazoyl penicillin which 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 have 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 fewer 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 them all because hypersensitivity is related to the basic penicillin structure; moreover, about 10% of penicillin-sensitive patients will be allergic to cefalosporins 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.

Benzylpenicillins 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 decreased sensitivity to penicillins such as 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 is slowly absorbed over a period of 12 hours to several days. They are the preferred choice 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.

Amoxicillin, amoxicillin with clavulanic acid, ampicillin and cloxacillin

Amoxicillin 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. Amoxicillin 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 gonorrhoea 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 *Haemophilus 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 **amoxicillin** widens amoxicillin's spectrum of activity and allows its use against amoxicillin-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, or genitourinary tract are not entered. This would include herniorrhaphy, cardiac, vascular, neurological, orthopaedic, and breast surgery. Cefazolin is also used for prophylaxis in surgery where contamination can be controlled, for example, in caesarian section and abdominal hysteroscopy.

Cefixime, **ceftazidime,** and **ceftriaxone** are third generation cefalosporins. Cefixime is orally active and is used for the treatment of uncomplicated gonorrhoea. Ceftriaxone is used for serious infections such as septicaemia, 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 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.

Amoxicillin

Capsule or tablet: 250 mg; 500 mg (anhydrous).
Powder for oral liquid: 125 mg (anhydrous)/5 ml.

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; gynaecological infections; gonorrhoea; 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 4); erythematous rash common in glandular fever, cytomegalovirus infection, chronic lymphatic leukaemia, and sometimes in HIV infection; maintain adequate hydration with high doses (risk of crystalluria); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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

Dental abscess (short course), *by mouth*, **ADULT,** 3 g repeated once after 8 hours.

Urinary tract infections (short course), *by mouth*, **ADULT,** 3 g repeated once after 10–12 hours.

Uncomplicated genital chlamydial infection, non-gonococcal urethritis, *by mouth,* **ADULT,** 500 mg every 8 hours for 7 days.

Gonorrhoea (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, diarrhoea; rash (hypersensitivity or toxic response; may be indicative of a serious reaction – discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, and interstitial nephritis (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).

Amoxicillin + clavulanic acid

Tablet: 500 mg + 125 mg.

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

Contraindications: hypersensitivity to penicillins (see introductory note above); history of penicillin- or amoxicillin with clavulanic acid-associated jaundice or hepatic dysfunction.

Precautions: history of allergy to penicillins (see introductory note above); renal impairment (Appendix 4); erythematous rash (common in glandular fever, cytomegalovirus infection), chronic lymphatic leukaemia, and possibly HIV infection; maintain adequate hydration with high doses (risk of crystalluria); hepatic impairment (Appendix 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

Dose:

NOTE. All doses expressed as amoxicillin.

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 hours.

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 to 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, diarrhoea; rash (hypersensitivity or toxic response; may be indicative of a serious reaction – discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-type reactions, haemolytic anaemia, 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

Powder for injection: 500 mg; 1 g (as sodium salt) in vial.

Uses: mastoiditis; gynaecological infections; septicaemia; peritonitis; endocarditis; meningitis; cholecystitis; osteomyelitis.

Contraindications: hypersensitivity to penicillins (see introductory note above).

Precautions: history of allergy (see introductory note above); renal impairment (Appendix 4); erythematous rash (common in glandular fever, acute or chronic lymphatic leukaemia, and cytomegalovirus infection); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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, 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, diarrhoea; rash (hypersensitivity or toxic response; may be indicative of a serious reaction — discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, and interstitial nephritis (see also introductory note above); rarely antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders.

Benzathine benzylpenicillin

Powder for injection: 1.44 g benzylpenicillin (= 2.4 million IU) in 5-ml vial.

Uses: streptococcal pharyngitis; diphtheria; syphilis and other treponemal infections (yaws, pinta, bejel); 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 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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

Yaws, pinta, bejel, *by deep intramuscular injection*, **ADULT,** 900 mg as a single dose; **CHILD,** 450 mg as a single dose.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: hypersensitivity reactions including urticaria, fever, joint pains, rash, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, and interstitial nephritis (see also introductory note above); neutropenia, thrombocytopenia, coagulation disorders; rarely central nervous system toxicity (associated with high dosage or severe renal failure); Jarisch-Herxheimer reaction (during treatment for syphilis and other spirochaete infections, probably due to release of endotoxins); rarely non-allergic (embolic–toxic) reactions; pain and inflammation at injection site.

Benzylpenicillin

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

Also known as penicillin G.

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 4); heart failure; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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; *by intramuscular injection* or *slow intravenous injection*, **CHILD** over 2 years, 120–180 mg/kg (maximum, 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, haemolytic anaemia, and interstitial nephritis (see also introductory notes above); diarrhoea, 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 spirochaete infections, probably due to release of endotoxins); inflammation, phlebitis or thrombophlebitis at injection sites.

Cefazolin

Powder for injection: 1 g (as sodium salt) in vial.

Uses: prophylaxis of infection in surgery.

Contraindications: hypersensitivity to cefalosporins.

Precautions: sensitivity to Beta Lactam antibacterials (avoid if history of immediate hypersensitivity reactions; see introductory note above); moderate renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); use may result in false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; **interactions**: Appendix 1.

Dose:

Surgical prophylaxis, *by deep intramuscular injection*, *by intravenous injection* (over at least 3–5 minutes), or *by intravenous infusion*, **ADULT,** 1 g as a single dose at induction of anaesthesia, or after cord clamping in caesarean section, repeated if necessary if surgery lasts over 3 hours; **CHILD,** 25 mg/kg

(maximum, 1 g) as a single dose at induction of anaesthesia, repeated if necessary if surgery lasts over 3 hours.

NOTE. Further doses may be given every 6–8 hours post-operatively for 24 hours if necessary, or for up to 5 days in continued risk of infection (consult manufacturer's literature).

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions; intramuscular administration may be painful and should be avoided where possible.

Adverse effects: diarrhoea, nausea, rash, electrolyte disturbances, cholestatic hepatitis, pain and inflammation at injection site; antibiotic-associated colitis; less commonly vomiting, headache, dizziness, and fever; rarely confusion (particularly following large doses and in renal impairment), arthritis, serum sickness-like reactions, neurotoxicity (including seizures), blood disorders (including neutropenia, eosinophilia, thrombocytopenia, leucopenia, thrombocythaemia, haemolytic anaemia, and bleeding), renal impairment (including interstitial nephritis), allergic reactions (including urticaria, anaphylaxis, angioedema, and bronchial obstruction), and abnormal liver function tests; erythema multiforme and toxic epidermal necrolysis also reported.

Cefixime

Capsule: 400 mg.

Uses: uncomplicated gonorrhoea.

Contraindications: hypersensitivity to cefalosporins.

Precautions: sensitivity to Beta Lactam antibacterials (avoid if history of **immediate** hypersensitivity reaction; see introductory note above); moderate renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); use may result in false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; **interactions**: Appendix 1.

Dose:

Uncomplicated anogenital gonorrhoea, *by mouth*, **ADULT,** 400 mg as a single dose.

Adverse effects: diarrhoea, nausea and vomiting, abdominal discomfort, headache; rarely antibiotic-associated colitis (particularly with higher doses); allergic reactions including rash, pruritus, urticaria, serum sickness-like reactions, fever and arthralgia, and anaphylaxis; erythema multiforme and toxic epidermal necrolysis reported; transient hepatitis, cholestatic jaundice; eosinophilia and blood disorders (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia); reversible

interstitial nephritis, hyperactivity, nervousness, sleep disturbances, hallucinations, confusion, hypertonia, and dizziness.

Ceftazidime

Powder for injection: 250 mg (as pentahydrate) in vial.

Ceftazidime is a complementary list antibacterial drug for use only when there is significant resistance to other medicines on the WHO Model List.

Uses: infections due to sensitive bacteria, especially those due to *Pseudomonas* spp. and those resistant to aminoglycosides.

Contraindications: hypersensitivity to cefalosporins; porphyria.

Precautions: sensitivity to Beta Lactam antibacterials (avoid if history of immediate hypersensitivity reaction; see introductory note above); renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); use may result in false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; **interactions**: Appendix 1.

Dose:

Infections due to susceptible organisms, *by deep intramuscular injection, by intravenous injection,* or *by intravenous infusion*, **ADULT,** 1 g every 8 hours or 2 g every 12 hours; in severe infections (including in the immunocompromised), 2 g every 8–12 hours or 3 g every 12 hours (in the elderly, usual maximum, 3 g daily); **NEONATE** and **INFANT** up to 2 months, 25–60 mg/kg daily in 2 divided doses; **CHILD** over 2 months, 30–100 mg/kg daily in 2–3 divided doses (intravenous route recommended for children).

Pseudomonal lung infection in cystic fibrosis, *by deep intramuscular injection*, *by intravenous injection,* or *by intravenous infusion*, **ADULT,** 100–150 mg/kg daily in 3 divided doses.

Infections in the immunocompromised, cystic fibrosis, or meningitis, *by intravenous injection* or *intravenous infusion*, **CHILD** over 2 months up to 150 mg/kg daily in 3 divided doses (maximum, 6 g daily).

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions. Intramuscular doses over 1 g should be divided between more than one site.

Adverse effects: diarrhoea, nausea and vomiting, abdominal discomfort, headache; rarely antibiotic-associated colitis (particularly with higher doses); allergic reactions including rash, pruritus, urticaria, serum sickness-like reactions, fever and arthralgia, and anaphylaxis; erythema multiforme and toxic epidermal necrolysis reported; transient hepatitis, cholestatic jaundice; eosinophilia and blood disorders (including thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia); reversible

interstitial nephritis; nervousness, sleep disturbances, confusion, hypertonia, and dizziness.

Ceftriaxone

Powder for injection: 250 mg; 1 g (as sodium salt) in vial.

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

Ceftriaxone is a complementary list medicine for use only when there is significant resistance to other antibacterial medicines on the WHO Model List.

Uses: serious infections due to sensitive bacteria, including septicaemia, pneumonia, and meningitis; osteomyelitis, septic arthritis; *Haemophilus influenzae* epiglottis; surgical prophylaxis; prophylaxis of meningococcal meningitis; shigellosis, invasive salmonellosis; endocarditis; gonococcal conjunctivitis; gonorrhoea; pelvic inflammatory disease; Lyme disease.

Contraindications: hypersensitivity to cefalosporins; porphyria; neonates with jaundice, hypoalbuminaemia, 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 4); hepatic impairment if accompanied by renal impairment (Appendix 5); 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 breastfeeding (but appropriate to use, see Appendices 2 and 3); false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; **interactions**: Appendix 1.

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); *by intravenous infusion* (over 60 minutes), **NEONATE,** 20–50 mg/kg daily (maximum, 50 mg/kg daily).

Uncomplicated gonorrhoea 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 (maximum, 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: diarrhoea, nausea and vomiting, abdominal discomfort, headache; rarely antibiotic-associated colitis (particularly with higher doses); allergic reactions including rash, pruritus, urticaria, serum sickness-like reactions, fever and arthralgia, and anaphylaxis; erythema multiforme and toxic epidermal necrolysis reported; transient hepatitis, cholestatic jaundice; eosinophilia and blood disorders (including thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, hallucinations, confusion, hypertonia and dizziness; calcium ceftriaxone precipitates in the urine (particularly in the very young, the dehydrated, or in those who are immobilized) or in the gallbladder (consider discontinuation if symptomatic); rarely prolongation of prothrombin time and pancreatitis.

Cloxacillin

Capsule: 500 mg; 1 g (as sodium salt).
Powder for injection: 500 mg (as sodium salt) in vial.
Powder for oral liquid: 125 mg (as sodium salt)/5 ml.

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

Uses: infections due to beta-lactamase-producing staphylococci including impetigo, cellulitis, and other soft-tissue infections; pyomyositis; staphylococcal endocarditis, septicaemia, 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 4) and hepatic impairment (Appendix 5); heart failure; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

Dose:

Infections due to susceptible beta-lactamase-producing staphylococci, **ADULT,** *by mouth*, 500 mg 4 times daily, doubled in severe infection; *by intramuscular injection*, 250 mg every 4–6 hours, doubled in severe infection; *by slow intravenous injection* or *by intravenous infusion*, 1–2 g every 6 hours; **CHILD** up to 2 years, quarter the adult dose; **CHILD** 2–10 years, half the adult dose.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: nausea and vomiting, diarrhoea; hypersensitivity reactions including urticaria, fever, joint pain, rash, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, 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.

Imipenem + cilastatin

Powder for injection: 250 mg (as monohydrate) + 250 mg (as sodium salt); 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial.

Imipenem with cilastatin is a complementary list antibacterial combination for use only when there is significant resistance to other medicines on the WHO Model List.

Uses: severe aerobic and anaerobic Gram-positive and Gram-negative infections in hospital (not indicated for CNS infections), including infections caused by resistant *Pseudomonas* and *Acinetobacter* spp.

Precautions: sensitivity to Beta Lactam antibacterials (avoid if history of immediate hypersensitivity reaction; see introductory note above); renal impairment (Appendix 4); central nervous system disorders, such as epilepsy; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

Dose:

NOTE. All doses are in terms of imipenem.

Infections due to susceptible organisms, *by intravenous infusion*, **ADULT,** 1–2 g daily in 3–4 divided doses; less susceptible organisms, **ADULT,** up to 50 mg/kg daily (maximum, 4 g daily) in 3–4 divided doses; **CHILD** over 3 months, 60 mg/kg daily (maximum, 2 g daily) in 4 divided doses; **CHILD** over 40 kg, adult dose.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

The intramuscular preparation must **not** be administered intravenously.

The infusion preparation must **not** be administered intramuscularly.

Adverse effects: nausea, vomiting, and diarrhoea; antibiotic-associated colitis; taste disturbances; tooth or tongue discoloration, hearing loss; blood disorders, positive Coombs' test; allergic reactions including rash, pruritus, urticaria, erythema multiforme (Stevens-Johnson syndrome), fever, and anaphylactic reactions; rarely toxic epidermal necrolysis, and exfoliative dermatitis; myoclonic activity, convulsions, confusion, and mental disturbances; slight increase in liver enzymes and bilirubin, rarely hepatitis; increases in serum creatinine and blood urea; red coloration of urine in children; erythema, pain and induration, and thrombophlebitis at injection sites.

Phenoxymethylpenicillin

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

Also known as penicillin V.

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 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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 diarrhoea.

Procaine benzylpenicillin

Powder for injection: 1 g (= 1 million IU); 3 g (= 3 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 note above); renal failure (Appendix 4); breastfeeding (Appendix 3); **interactions**: Appendix 1.

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, haemolytic anaemia, 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 spirochaete infections, probably due to release of endotoxins); rarely, non-allergic (embolic–toxic) reactions; pain and inflammation at injection site.

6.2.2 Other antibacterials

Azithromycin

Capsule: 250 mg or 500 mg.
Oral liquid: 200 mg/5 ml.

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 gonorrhoea because macrolide resistance emerges rapidly when it is used under these circumstances.

Uses: uncomplicated genital chlamydial infections and trachoma.

Contraindications: hepatic impairment (Appendix 5).

Precautions: pregnancy (Appendix 2) and breastfeeding (Appendix 3); prolongation of QT interval (ventricular tachycardia reported); **interactions**: Appendix 1.

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); also anorexia, dyspepsia, flatulence, constipation, pancreatitis; syncope, dizziness, headache, drowsiness, agitation, anxiety, hyperactivity; photosensitivity; hepatitis, interstitial nephritis, acute renal failure, asthenia, paraesthesia, arthralgia, convulsions, mild neutropenia, thrombocytopenia, tinnitus, hepatic necrosis, hepatic failure, tongue discoloration, and taste disturbances.

Chloramphenicol

Capsule: 250 mg.
Oily suspension for injection: 0.5 g (as sodium succinate)/ml in 2-ml ampoule.
Oral liquid: 150 mg (as palmitate)/5 ml.
Powder for injection: 1 g (sodium succinate) in vial.

Chloramphenicol is a potent broad-spectrum antibiotic. However, it is associated with serious haematological adverse effects and should be reserved for the treatment of severe infections, particularly those caused by *Haemophilus 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.

Uses: severe life-threatening infections, particularly those caused by *Haemophilus influenzae* and typhoid fever; also, pneumonia; cerebral abscess; mastoiditis; rickettsia; relapsing fever; gangrene; granuloma inguinale; listeriosis; plague; psitticosis; tularaemia; Whipple disease; septicaemia; meningitis.

Contraindications: pregnancy (Appendix 2); porphyria.

Precautions: avoid repeated courses and prolonged use; hepatic impairment (reduce dose; Appendix 5); severe renal impairment (reduce dose; Appendix 4); blood counts required before and during treatment; monitor plasma concentrations in neonates (see below); breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Infections due to susceptible organisms which 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, septicaemia, and *haemophilus* 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/litre; pre-dose 'trough' concentration should not exceed 15 mg/litre.

Adverse effects: bone marrow depression—reversible and irreversible aplastic anaemia (with reports of leukaemia), anaemia, leukopenia, and thrombocytopenia; nocturnal haemoglobinuria; peripheral neuritis and optic neuritis; nausea, vomiting, diarrhoea, dry mouth, stomatitis, glossitis; headache, depression; hypersensitivity reactions including rash, urticaria, fever, angioedema, and rarely anaphylaxis; grey syndrome (vomiting, greenish diarrhoea, 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

Tablet: 250 mg (as hydrochloride).

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.

Ciprofloxacin is a representative quinolone antibacterial. Various medicines can serve as alternatives.

Uses: gastroenteritis (including cholera, shigellosis, travellers' diarrhoea, campylobacter, and salmonella enteritis); typhoid; gonorrhoea; 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; septicaemia; anthrax; skin infections; otitis externa; prophylaxis in surgery.

Contraindications: history of tendon disorders related to quinolone use (see below).

Precautions: history of epilepsy or conditions that predispose to seizures, G6PD deficiency, myasthenia gravis (risk of exacerbation), pregnancy (Appendix 2) and breastfeeding (Appendix 3), children or adolescents (see below); avoid exposure to excessive sunlight (discontinue if photosensitivity occurs); rarely tendon damage (see below); renal impairment (Appendix 4); avoid excessive alkalinity of urine and ensure adequate fluid intake (risk of crystalluria); **interactions**: Appendix 1.

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. May impair ability to perform skilled tasks, for example, operating machinery or driving.

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.

Gonorrhoea 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 (maximum, 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, diarrhoea (rarely antibiotic-associated colitis); pancreatitis, dysphagia, tremor, hyperglycaemia, headache, dizziness, sleep disorders, rash (rarely erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis), pruritus; vasculitis, erythema nodosum, petechiae, haemorrhagic bullae; less frequently anorexia and increased blood urea and creatinine; drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, paraesthesia, 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, oedema, syncope, hot flushes and sweating; also isolated reports of tendon inflammation and damage (especially in the elderly and in those taking corticosteroids; see also above), haemolytic anaemia, renal failure, interstitial nephritis, and hepatic dysfunction (including hepatitis and cholestatic jaundice); discontinue if psychiatric, neurological, or hypersensitivity reactions (including severe rash) occur.

Clindamycin

Capsule: 150 mg.
Injection: 150 mg (as phosphate)/ml.

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 diarrhoea 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 a penicillin is not appropriate.

Clindamycin is a complementary list medicine for use when penicillin is not appropriate.

Uses: staphylococcal bone and joint infections, pyomyositis; necrotizing fasciitis; peritonitis; endocarditis prophylaxis; pelvic inflammatory disease (with gentamicin); pneumonia.

Contraindications: diarrhoeal states; avoid injections containing benzyl alcohol in neonates; porphyria.

Precautions: discontinue immediately if diarrhoea or colitis develop; hepatic impairment (Appendix 5); renal impairment (Appendix 4); monitor liver and renal function on prolonged therapy and in neonates and infants; the elderly; females; pregnancy (Appendix 2) and breastfeeding (Appendix 3); avoid rapid intravenous administration; **interactions:** Appendix 1.

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 anaesthetic), *by mouth*, **ADULT,** 600 mg, 1 hour before procedure.

Endocarditis prophylaxis (for procedures under general anaesthetic), *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 diarrhoea develops; capsules should be swallowed with a glass of water.

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: diarrhoea (discontinue treatment); nausea, vomiting, abdominal discomfort, oesophagitis, 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

Capsule or tablet: 100 mg (hydrochloride).

Doxycycline is a tetracycline and is a broad-spectrum antibiotic that is effective for conditions caused by chlamydia, rickettsia, brucella, and the spirochaete, *Borrelia burgdorferi* (Lyme disease). It is the preferred tetracycline since it has a more favourable pharmacokinetic profile than other tetracyclines, including tetracycline. It is deposited in growing bone and teeth causing staining and occasionally dental hypoplasia. It should not be given to children under 8 years or pregnant women; in some countries, use in children under 12 years is contraindicated.

Uses: supplement to quinine or artesunate treatment for multidrug-resistant *P. falciparum* malaria; short-term prophylaxis of multidrug-resistant *P. falciparum* malaria; see also notes above; bacterial infections (section 6.2.2).

Contraindications: pregnancy (Appendix 2); children under 8 years; porphyria; systemic lupus erythematosus.

Precautions: avoid exposure to sunlight or sunlamps (photosensitivity reported); renal impairment (Appendix 4); hepatic impairment (Appendix 5); breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Supplement to malaria treatment (see note above), *by mouth*, **ADULT** and **CHILD** over 8 years, 100 mg twice daily for 7–10 days.

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.

PATIENT ADVICE. Capsules should be swallowed whole with plenty of fluid while sitting or standing to prevent oesophageal irritation. May be given with food or milk to counter gastric irritation.

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

Capsule or tablet: 250 mg (as stearate or ethyl succinate).
Powder for injection: 500 mg (as lactobionate) in vial.
Powder for oral liquid: 125 mg (as stearate or ethyl succinate).

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. It is effective in respiratory infections, whooping cough, legionnaires' disease, and campylobacter enteritis.

Erythromycin is a representative macrolide antibiotic. Various medicines can serve as alternatives.

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 5) and renal impairment (Appendix 4); predisposition to QT interval prolongation (including electrolyte disturbances and concomitant use of drugs that prolong the QT interval); pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1.

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, diarrhoea, 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

Injection: 10 mg; 40 mg (as sulfate)/ml in 2-ml vial.

Aminoglycosides including gentamicin are bactericidal and active against some Gram-positive and many Gram-negative organisms including *Pseudomonas aeruginosa*. Aminoglycosides are not absorbed from the gut and must therefore be given by injection for systemic infections. Excretion is mainly by the kidney and accumulation occurs in renal impairment.

Gentamicin should only be prescribed and administered by trained health personnel. Care must be taken to ensure correct dosage and duration of treatment are not exceeded, because most adverse effects are dose related. The most important adverse effects are ototoxicity and nephrotoxicity and they are most common in the elderly and in patients with renal impairment. These groups and, if possible, all patients should be monitored for ototoxicity by audiometry. If there is impairment of renal function, the dose interval must be increased; in severe renal impairment, the dose should also be reduced. Serum concentration monitoring avoids both excessive and subtherapeutic concentrations and can prevent toxicity and ensure efficacy. If possible serum concentrations should be monitored in all patients, but **must** be measured in infants, the elderly, in obesity, in cystic fibrosis, in high-dosage regimens, in renal impairment, or if treatment lasts for longer than 7 days.

Loading and maintenance doses of gentamicin are based on the patient's weight and renal function (for example, using a nomogram) with adjustments based on plasma gentamicin concentration. High doses are used occasionally for serious infections.

Gentamicin is a representative aminoglycoside antibiotic. Various medicines can serve as alternatives.

Uses: pneumonia; cholecystitis; peritonitis; septicaemia; acute pyelonephritis; prostatitis; otitis externa; skin and soft tissue infections; pelvic inflammatory

disease (with clindamycin); endocarditis; meningitis; listeriosis; tularaemia; brucellosis; plague; surgical prophylaxis; eye infections (section 21.1).

Contraindications: myasthenia gravis.

Precautions: renal impairment (reduce dose; Appendix 4); 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 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

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/litre (3–5 mg/litre for endocarditis); pre-dose (trough) concentration should be less than 2 mg/litre (less than 1 mg/litre 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

Injection: 500 mg in 100-ml vial.
Oral liquid: 200 mg (as benzoate)/5 ml.
Suppository: 500 mg; 1 g.
Tablet: 200-500 mg.

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.

Metronidazole is a representative antibacterial and antiprotozoal drug. Various medicines can serve as alternatives.

Uses: anaerobic bacterial infections, including gingivitis and other oral infections, pelvic inflammatory disease (with doxycycline and either ciprofloxacin or ceftriaxone; section 6.2.1), tetanus, septicaemia, 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 disease (section 17.3).

Contraindications: chronic alcohol dependence.

Precautions: disulfiram-like reaction with alcohol; hepatic impairment and hepatic encephalopathy (Appendix 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3); clinical and laboratory monitoring recommended in courses lasting longer than 10 days; **interactions:** Appendix 1.

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.

Anaerobic infections, *by rectum*, **ADULT** and **CHILD** over 10 years, 1 g every 8 hours for 3 days, then 1 g every 12 hours; **CHILD** up to 1 year, 125 mg every 8 hours for 3 days, then every 12 hours; **CHILD** 1–5 years, 250 mg; **CHILD** 5–10 years, 500 mg.

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 rectum*, **ADULT,** 1 g 2 hours before surgery; up to 3 further doses of 1 g may be given every 8 hours for high-risk procedures; **CHILD** 5–10 years, 500 mg 2 hours before surgery; up to 3 further doses of 500 mg may be given every 8 hours for high-risk procedures.

Surgical prophylaxis *by intravenous infusion* (if rectal administration inappropriate), **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 one 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.

Nitrofurantoin

Tablet: 100 mg.

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.

Uses: urinary tract infections.

Contraindications: impaired renal function (Appendix 4); infants less than 3 months; G6PD-deficiency including breastfeeding of affected infants (Appendix 3); pregnancy at term (Appendix 2); porphyria.

Precautions: pulmonary disorders; hepatic impairment (Appendix 5); monitor lung and liver function on long-term therapy (discontinue if lung function deteriorates); neurological or allergic disorders; anaemia; diabetes mellitus; the elderly and debilitated; vitamin B and folate deficiency; use may result in false positive urinary glucose (if testing for reducing substances); urine may be coloured 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.

Spectinomycin

Powder for injection: 2 g (as hydrochloride) in vial.

Spectinomycin is active against Gram-negative organisms including *Neiserria gonorrhoea*. It is not suitable for the treatment of syphilis and patients being treated for gonorrhoea should be observed for evidence of syphilis. It should be used only when alternative therapies are inappropriate.

Uses: uncomplicated and disseminated gonorrhoea; adult and neonatal gonococcal conjunctivitis; chancroid.

Precautions: renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Dose:

Uncomplicated gonococcal infections and chancroid, *by deep intramuscular injection*, **ADULT,** 2 g as a single dose; increased to 4 g as a single dose divided between 2 injection sites in difficult to treat cases and where there is known antibiotic resistance.

Disseminated gonococcal infections, *by deep intramuscular injection*, **ADULT,** 2 g twice daily for 7 days.

Neonatal gonococcal conjunctivitis, *by deep intramuscular injection*, **NEONATE,** 25 mg/kg (maximum, 75 mg) as a single dose.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: nausea, headache, dizziness, fever, chills, insomnia, urticaria; rarely, anaphylaxis; pain at injection site.

Sulfadiazine

Injection: 250 mg (sodium salt) in 4-ml ampoule.
Tablet: 500 mg.

The usefulness of sulfonamides is limited by an increasing incidence of bacterial resistance. For many indications, they have been replaced by antibiotics that are more active and safer. Sulfadiazine is, however, still used in the prevention of rheumatic fever recurrence.

Sulfadiazine is a complementary list antibacterial medicine.

Uses: prevention of recurrences of rheumatic fever; toxoplasmosis (section 6.5.4)

Contraindications: hypersensitivity to sulfonamides; porphyria

Precautions: hepatic impairment (avoid if severe; Appendix 5); renal impairment (avoid if severe; Appendix 4); 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; the elderly; asthma; G6PD deficiency; pregnancy (Appendix 2) and breastfeeding (Appendix 3); avoid in infants under 6 weeks; **interactions:** Appendix 1.

Dose:

Prevention of recurrences of rheumatic fever, *by mouth*, **ADULT,** 1 g daily; **CHILD,** 500 mg daily.

Adverse effects: nausea, vomiting, diarrhoea, headache; hypersensitivity reactions including rash, pruritus, photosensitivity reactions, exfoliative dermatitis, and erythema nodosum; rarely erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis; systemic lupus erythematosus, myocarditis, serum sickness; crystalluria — resulting in haematuria, oliguria, and anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, and purpura (discontinue immediately); liver damage, pancreatitis, antibiotic-associated colitis, eosinophilia, cough and shortness of breath, pulmonary infiltrates, aseptic meningitis, depression, convulsions, ataxia, tinnitus, vertigo, dizziness, hallucinations, and electrolyte disturbances also reported.

Sulfamethoxazole + trimethoprim

Injection: 80 mg + 16 mg/ml in 5-ml and 10-ml ampoules.
Oral liquid: 200 mg + 40 mg/5 ml.
Tablet: 100 mg + 20 mg; 400 mg + 80 mg.

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 (section 6.5.4).

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 4); hepatic impairment (avoid if severe; Appendix 5); 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 hyperkalaemia, the elderly; asthma; G6PD deficiency; pregnancy (Appendix 2) and breastfeeding (Appendix 3); avoid in infants under 6 weeks; **interactions:** Appendix 1.

Dose:

Infections due to susceptible organisms (which 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, diarrhoea; headache; hyperkalaemia; 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, hypoglycaemia, blood disorders (including leukopenia, thrombocytopenia, megaloblastic anaemia, and eosinophilia), hyponatraemia, renal disorders (including interstitial nephritis), arthralgia, myalgia, vasculitis, and systemic lupus erythematosus.

Trimethoprim

Tablet: 100 mg; 200 mg.

Trimethoprim is also used alone for respiratory tract infections, in particular for bronchitis, and for urinary tract infections.

Uses: urinary tract infections; bronchitis.

Contraindications: blood disorders; porphyria.

Precautions: renal impairment (avoid if severe, Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); predisposition to folate deficiency; the elderly; monitor blood counts on long-term therapy (but practical value not proven); neonates (specialist supervision required); **interactions:** Appendix 1.

Dose:

Acute infections, *by mouth*, **ADULT,** 200 mg every 12 hours; **CHILD** 6 weeks–5 months, 25 mg twice daily; **CHILD** 6 months–5 years, 50 mg twice daily; **CHILD** 6–12 years, 100 mg twice daily.

Acute infections, *by slow intravenous injection* or *by intravenous infusion*, **ADULT,** 200 mg every 12 hours; **CHILD** under 12 years, 8 mg/kg daily in 2–3 divided doses.

Chronic infections and prophylaxis, *by mouth*, **ADULT,** 100 mg at night; **CHILD,** 1–2 mg/kg at night.

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: rash, pruritus; depression of haematopoiesis; gastrointestinal disturbances including nausea and vomiting; hyperkalaemia; rarely erythema multiforme and toxic epidermal necrolysis; photosensitivity and other allergic reactions including angioedema and anaphylaxis; aseptic meningitis.

Vancomycin

Powder for injection: 250 mg (as hydrochloride) in vial.

Vancomycin is not significantly absorbed from the gastrointestinal tract and must be given intravenously for systemic infections which cannot be treated with other effective, less toxic antimicrobials. It is used to treat serious infections due to Gram-positive cocci including meticillin-resistant staphylococcal infections, brain abscess, meningitis, and septicaemia and should be used in a hospital setting only.

Vancomycin is a complementary list antibacterial medicine for use only when there is significant resistance to other medicines on the WHO Model List.

Uses: meticillin-resistant staphylococcal pneumonia; septicaemia related to vascular catheter; meningitis; antibiotic-associated colitis; endocarditis prophylaxis (with gentamicin).

Precautions: avoid rapid infusion (risk of anaphylactoid reactions, see Adverse effects); rotate infusion sites; renal impairment (Appendix 4); the elderly; history of deafness (avoid); monitor plasma vancomycin concentration after 3 or 4 doses (earlier in the elderly and in renal impairment), blood counts, urine, and renal function; monitor auditory function in the elderly or in renal impairment; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Serious staphylococcal infections, *by intravenous infusion*, **ADULT,** 500 mg over at least 60 minutes every 6 hours or 1 g over at least 100 minutes every 12 hours; **ELDERLY** (over 65 years), 500 mg every 12 hours or 1 g once daily; **NEONATE** up to 1 week, 15 mg/kg initially, then 10 mg/kg every 12 hours; **NEONATE** 1–4 weeks, 15 mg/kg initially, then 10 mg/kg every 8 hours; **CHILD** over 1 month, 10 mg/kg every 6 hours.

Antibiotic-associated colitis, *by mouth*, **ADULT,** 125–500 mg every 6 hours for 7–10 days; **CHILD** 1 month–5 years, 5 mg/kg every 6 hours; **CHILD** over 5 years, 62.5 mg every 6 hours.

NOTE. Injection can be used to prepare a solution for oral administration.

Endocarditis prophylaxis (for procedures under general anaesthetic), *by intravenous infusion*, **ADULT,** 1 g over at least 100 minutes, then gentamicin 120 mg at induction or 15 minutes before procedure.

RECONSTITUTION AND ADMINISTRATION. According to the manufacturer's directions.

NOTE. Peak plasma concentration (measured 2 hours after infusion) should not exceed 30 mg/litre; pre-dose (trough) concentration should not exceed 5–10 mg/litre (10–15 mg/litre in endocarditis).

Adverse effects: nephrotoxicity including renal failure and interstitial nephritis; ototoxicity (discontinue if tinnitus occurs); blood disorders; nausea, chills, fever, eosinophilia, anaphylaxis, rash, including exfoliative dermatitis,

erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis, and vasculitis; phlebitis; severe hypotension (with shock and cardiac arrest), wheezing, dyspnoea, urticaria, pruritus, flushing of the upper body ('red man' syndrome), pain, and muscle spasm of the back and chest on rapid infusion.

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 programmes 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 used in 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 in colour-coded blister packs (MDT blister packs) to improve patients' adherence to treatment. Any patient with a positive skin smear should be treated with the oral multidrug therapy (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 multidrug therapy 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 only in MB leprosy. 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 hospital.

If a patient does not respond to lepra reaction treatment within 6 weeks or their condition worsen, the patient must be sent immediately to the nearest specialist centre. 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 centre treatment is required.

Treatment regimens

The recommended regimen for paucibacillary 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 multibacillary (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 [not included on the 15th WHO Model List].

Clofazimine

Capsule: 50 mg; 100 mg.

Uses: multibacillary (MB) leprosy; type 2 lepra reactions.

Precautions: pre-existing gastrointestinal symptoms (reduce dose; increase dose interval or discontinue if symptoms develop during treatment); liver and renal impairment; pregnancy (Appendix 2); and breastfeeding (Appendix 3); may discolour 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, faeces, and urine; dose-related gastrointestinal symptoms including pain, nausea, vomiting, diarrhoea, weight loss, and gastrointestinal bleeding; severe mucosal and submucosal oedema, with prolonged treatment with high doses (may be severe enough to cause subacute 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

Tablet: 25 mg; 50 mg; 100 mg.

Uses: paucibacillary (PB) and multibacillary (MB) leprosy.

Contraindications: hypersensitivity to sulfones; severe anaemia.

Precautions: anaemia (treat severe anaemia before commencement of therapy and monitor blood counts during treatment); susceptibility to haemolysis including G6PD deficiency (including breastfeeding affected infants); pregnancy (Appendix 2) and breastfeeding (Appendix 3); porphyria; **interactions:** Appendix 1.

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; see also introductory note above), *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 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: haemolysis and methaemoglobinaemia; 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, paraesthesia, reversible peripheral neuropathy, and psychoses reported.

Rifampicin

Capsule or tablet: 150 mg; 300 mg.

Uses: paucibacillary leprosy (PB); multibacillary leprosy (MB); meningitis; tuberculosis (section 6.2.4).

Contraindications: hypersensitivity to rifampicin; jaundice.

Precautions: hepatic impairment (reduce dose; Appendix 5); monitor liver function and blood counts in liver disorders, alcohol dependency, the elderly, and in those on prolonged therapy; renal impairment (if dose above 600 mg daily; Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); porphyria; discolours soft contact lenses; important: advise patients on oral contraceptives to use additional means; **interactions:** Appendix 1.

NOTE. Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, haemolysis, or thrombocytopenia; discontinue permanently if serious adverse effects occur.

LIVER DISORDERS. Patients or their 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 diarrhoea (antibiotic-associated colitis reported); headache, drowsiness; rash, fever, influenza-like syndrome and respiratory symptoms, collapse, shock, haemolytic anaemia, 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 maximum daily dose of 600 mg); oedema, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia, and menstrual disturbances also reported; urine, tears, saliva, and sputum coloured orange-red.

6.2.4 Antituberculosis medicines

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, 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) therapy, 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 was receiving a 3 times weekly or daily dose regimen. Therefore, there is a greater risk of treatment failure 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 two 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 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 the following tables 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 tuberculosis should be used in specialized centres adhering to WHO standards for TB control.

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. Preventative antituberculosis therapy of such persons is recommended.

Chemoprophylaxis with **isoniazid** can prevent the development of clinically apparent disease in persons in close contact with infectious 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 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 (see also section 19.3).

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 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 (see also section 19.1).

Recommended 6-month treatment regimens for tuberculosis[a]

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[b]	15 mg/kg daily	
or		
Ethambutol	15 mg/kg daily[c]	
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[b]	15 mg/kg 3 times weekly	
or		
Ethambutol	30 mg/kg 3 times weekly	

Recommended 8-month treatment regimen for tuberculosis[a]

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		
Streptomycin[b]	15 mg/kg daily	
or		
Ethambutol	15 mg/kg daily[c]	15 mg/kg daily

[a]Unless otherwise indicated, doses are suitable for both adults and children.
[b]Streptomycin always replaces ethambutol in meningeal TB.
[c]Ethambutol 20 mg/kg recommended in children.

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 weekly[2]):
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 which has relapsed, or failed[3] to respond, or if treatment was interrupted

Initial phase[1] (antibacterials administered daily or 3 times weekly):
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):
isoniazid + rifampicin + ethambutol for 5 months.

Category III: New smear-negative pulmonary disease (other than in Category I) and less severe extra-pulmonary disease

Initial phase[1] (antibacterials administered daily or 3 times weekly[2]):
isoniazid + rifampicin + pyrazinamide + ethambutol[4] 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 IV: Chronic and multidrug-resistant tuberculosis (MDR-TB) (smear-positive despite supervised re-treatment)[5]

specially designed standardized or individualized regimens recommended

Amikacin

Powder for injection: 1000 mg in vial.

Amikacin is a complementary list medicine for the treatment of multidrug-resistant tuberculosis which should be used in specialized centres adhering to WHO standards for tuberculosis control.

Capreomycin

Powder for injection: 1000 mg in vial.

Capreomycin is a complementary list medicine for the treatment of multidrug-resistant tuberculosis which should be used in specialized centres adhering to WHO standards for tuberculosis control.

Cycloserine

Capsule or tablet: 250 mg.

Cycloserine is a complementary list medicine for the treatment of multidrug-resistant tuberculosis which should be used in specialized centres adhering to WHO standards for tuberculosis control.

Ethambutol

Tablet: 100-400 mg (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/minute; Appendix 4); the elderly; pregnancy (Appendix 2); breastfeeding (Appendix 3).

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 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/litre (7–22 micromol/litre); trough (pre-dose) concentration should be less than 1 mg/litre (4 micromol/litre).

Adverse effects: optic neuritis including reduced visual acuity and red/green colour blindness (early changes usually reversible; prompt withdrawal may prevent blindness); peripheral neuritis (especially in legs); gout; rarely rash, pruritus, urticaria, and thrombocytopenia.

Ethionamide

Tablet: 125 mg; 250 mg.

Ethionamide is a complementary list medicine for the treatment of multidrug-resistant tuberculosis which should be used in specialized centres adhering to WHO standards for tuberculosis control.

Isoniazid

Tablet: 100-300 mg.
Tablet (scored): 50 mg.

Uses: tuberculosis treatment, in combination with other drugs (see notes and tables above); tuberculosis prophylaxis.

Contraindications: drug-induced hepatic disease.

Precautions: hepatic impairment (monitor hepatic function; Appendix 5); malnutrition, chronic alcohol dependence, chronic renal failure (Appendix 4), diabetes mellitus, and HIV infection (prophylactic pyridoxine, 10 mg daily, required because of the increased risk of peripheral neuritis; see also section 27); epilepsy; slow acetylator status (increased risk of adverse effects); history of psychosis; pregnancy (Appendix 2); breastfeeding (Appendix 3); porphyria; **interactions:** Appendix 1.

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 above), *by mouth*, **ADULT** and **CHILD,** 5 mg/kg (4–6 mg/kg) daily (maximum, 300 mg daily), or 10 mg/kg 3 times weekly.

Tuberculosis, treatment in critically ill patients unable to take oral therapy (as part of a combination therapy), *by intramuscular injection*, **ADULT,** 200–300 mg as single daily dose; **CHILD,** 10–20 mg/kg daily.

Tuberculosis, prophylaxis, *by mouth*, **ADULT,** 300 mg daily for at least 6 months; **CHILD,** 5 mg/kg daily (maximum, 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, diarrhoea 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, haemolytic anaemia, and aplastic anaemia; optic neuritis, toxic psychoses, and convulsions; hepatitis (especially in those over the age of 35 years and in regular users of alcohol; withdraw treatment); systemic lupus erythematosus-like syndrome, pellagra, hyperreflexia, difficulty with micturition, hyperglycaemia, and gynaecomastia also reported.

Isoniazid + ethambutol

Tablet: 150 mg + 400 mg.

Uses: tuberculosis, in combination with other drugs.

Contraindications: combined preparation not suitable for use in children; see also under Ethambutol and Isoniazid.

Precautions: see under Ethambutol and Isoniazid.

Dose:

Tuberculosis (as part of an 8-month regimen; see introductory note and tables above), *by mouth*, **ADULT,** ethambutol, 800 mg and isoniazid, 300 mg daily

Adverse effects: see under Ethambutol and Isoniazid.

Kanamycin

Powder for injection: 1000 mg in vial.

Kanamycin is a complementary list medicine for the treatment of multidrug-resistant tuberculosis which should be used in specialized centres adhering to WHO standards for tuberculosis control.

Ofloxacin

Tablet: 200 mg; 400 mg.

Ofloxacin (and levofloxacin) are complementary list medicines for the treatment of multidrug-resistant tuberculosis which should be used in specialized centres adhering to WHO standards for tuberculosis control.

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p-aminosalicylic acid

Granules: 4 g in sachet.
Tablet: 500 mg.

p-aminosalicylic acid is a complementary list medicine for the treatment of multidrug-resistant tuberculosis which should be used in specialized centres adhering to WHO standards for tuberculosis control.

Pyrazinamide

Tablet: 400 mg.
Tablet (dispersible): 150 mg.
Tablet (scored): 150 mg.

Uses: tuberculosis, in combination with other drugs.

Contraindications: severe hepatic impairment; porphyria.

Precautions: hepatic impairment (monitor hepatic function; Appendix 5); renal impairment (Appendix 4); diabetes mellitus (monitor blood glucose — may change suddenly); gout; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

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 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 anaemia; rash, photosensitivity.

Rifampicin

Capsule or tablet: 150 mg; 300 mg.

Uses: tuberculosis, in combination with other drugs; leprosy (section 6.2.3); meningitis.

Contraindications: hypersensitivity to rifamycins; jaundice.

Precautions: hepatic impairment (reduce dose; Appendix 5); monitor liver function and blood counts in liver disorders, alcohol dependency, the elderly, and in those on prolonged therapy; renal impairment (if dose above 600 mg daily; Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); porphyria; discolours soft contact lenses; **important**: advise patients on hormonal contraceptives to use additional means; **interactions:** Appendix 1.

NOTE. Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, haemolysis, or thrombocytopenia — discontinue permanently if serious adverse effects occur.

LIVER DISORDERS. Patients or their 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:

Tuberculosis (as part of a 6- or 8-month regimen; see introductory notes and tables above), *by mouth*, **ADULT** and **CHILD,** 10 mg/kg daily or 3 times weekly (maximum, 600 mg daily).

PATIENT ADVICE. Take dose at least 30 minutes before a meal, as absorption is reduced when taken with food.

Adverse effects: severe gastrointestinal disturbances including anorexia, nausea, vomiting, and diarrhoea (antibiotic-associated colitis reported); headache, drowsiness; rash, fever, influenza-like syndrome and respiratory symptoms, collapse, shock, haemolytic anaemia, 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 maximum dose of 600 mg daily); oedema, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia, and menstrual disturbances also reported; urine, tears, saliva, and sputum coloured orange-red.

Rifampicin + isoniazid

Tablet:

60 mg + 30 mg; 150 mg + 75 mg; 300 mg + 150 mg.
60 mg + 60 mg (For intermittent use 3 times weekly).
150 mg + 150 mg (For intermittent use 3 times weekly).

Uses: tuberculosis, in combination with other drugs.

Contraindications: see under Isoniazid and Rifampicin.

Precautions: combined preparation usually not suitable for use in children; see also under Isoniazid and Rifampicin.

Dose:

Tuberculosis (as part of a 6-month regimen; see introductory note and tables 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 above), *by mouth*, **ADULT,** rifampicin, 10 mg/kg and isoniazid, 10 mg/kg, 3 times weekly.

Adverse effects: see under Isoniazid and Rifampicin.

Rifampicin + isoniazid + ethambutol

Tablet: 150 mg + 75 mg + 275 mg.

Uses: tuberculosis, in combination with other drugs.

Contraindications: see under Isoniazid, Ethambutol, and Rifampicin.

Precautions: combined preparation usually not suitable for use in children, see also under Isoniazid, Ethambutol, and Rifampicin.

Dose:

Tuberculosis (as part of an 8-month regimen; see introductory note and tables 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, and Rifampicin.

Rifampicin + isoniazid + pyrazinamide

Tablet:

60 mg + 30 mg + 150 mg; 150 mg + 75 mg + 400 mg.
150 mg + 150 mg + 500 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, and Rifampicin.

Precautions: see under Isoniazid, Pyrazinamide, and Rifampicin.

Dose:

Tuberculosis (as part of a 6-month regimen; see introductory note and tables 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, and Rifampicin.

Rifampicin + isoniazid + pyrazinamide + ethambutol

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, and Rifampicin.

Precautions: see under Ethambutol, Isoniazid, Pyrazinamide, and Rifampicin.

Dose:

Tuberculosis (as part of a 6-month regimen; see introductory note and tables 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, and Rifampicin.

Streptomycin

Powder for injection: 1 g (as sulfate) in vial.

Uses: tuberculosis, in combination with other drugs; tularaemia; plague; brucellosis (with doxycycline; section 6.2.2).

Contraindications: hearing disorders; myasthenia gravis; pregnancy (Appendix 2).

Precautions: children (painful injection, avoid use if possible); renal impairment (Appendix 4), infants, and the elderly (adjust dose and monitor renal, auditory, and vestibular function, and plasma streptomycin concentrations); breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Tuberculosis (as part of a 6- or 8-month regimen; see introductory note and tables 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. One-hour (peak) plasma concentration should be 15–40 mg/litre; pre-dose (trough) concentration should be less than 5 mg/litre (less than 1 mg/litre in renal impairment or those over 50 years).

Adverse effects: vestibular and auditory damage, nephrotoxicity; hypersensitivity reactions (withdraw treatment); paraesthesia of mouth; rarely hypomagnesaemia on prolonged therapy; antibiotic-associated colitis; also, nausea, vomiting, and rash; rarely haemolytic anaemia, aplastic anaemia, 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, and 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 against 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 candidosis.

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 only obtained after several months of continuous treatment. Lipid formulations of amphotericin B for intravenous infusion [not included on the 15th WHO Model List] are significantly less toxic, but are very much more expensive.

Clotrimazole is an imidazole antifungal which is effective in short courses for the treatment of vaginal candidosis. 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 (see also section 13.1), as well as in the management of superficial infections. Fluconazole is also used to prevent fungal infections in immunocompromised patients.

Flucytosine is a synthetic fluorinated pyrimidine with a narrow spectrum of antifungal activity, but which is particularly 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* (see also section 13.1). 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 it is not absorbed from the skin or mucous membranes when applied topically. It is used for the treatment of candidosis, but is less effective for prevention or treatment of candidosis 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 [not included on the 15th WHO Model List], by mouth has been tried as an alternative to potassium iodide in both cutaneous and extra-cutaneous sporotrichosis. In phycomycosis, **fluconazole** may be effective.

Amphotericin B

Powder for injection: 50 mg in vial.

Amphotericin B is a complementary list antifungal medicine.

Uses: life-threatening fungal infections including histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, aspergillosis, cryptococcosis, mucormycosis, sporotrichosis, and candidosis; leishmaniasis (section 6.5.2).

Precautions: initial test dose required (see note below); renal impairment (Appendix 4); monitor hepatic and renal function; blood counts, and plasma electrolyte concentrations (including potassium and magnesium concentration); pregnancy (Appendix 2) and breastfeeding (Appendix 3); avoid rapid infusion (risk of arrhythmias); **interactions:** Appendix 1.

ANAPHYLAXIS. Anaphylaxis rarely occurs with intravenous amphotericin B and a test dose is advisable before commencing the first infusion. The patient should be observed for about 30 minutes after the test dose.

Dose:

Systemic fungal infections, *by intravenous infusion*, **ADULT** and **CHILD,** initial test dose, 1 mg over 20–30 minutes, followed by 250 micrograms/kg daily, gradually increased up to 1 mg/kg daily, or in severe infection, up to 1.5 mg/kg daily or on alternate days.

NOTE. Prolonged treatment is usually necessary; if treatment is interrupted for longer than 7 days, it should be recommenced at 250 micrograms/kg daily and increased gradually.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: fever, headache, anorexia, weight loss, nausea and vomiting, malaise, diarrhoea, muscle and joint pain, dyspepsia, epigastric pain; renal function disturbances (including hypokalaemia, hypomagnesaemia, and renal toxicity); blood disorders; cardiovascular toxicity (including arrhythmias); neurological disorders (including peripheral neuropathy); abnormal liver function (discontinue treatment); rash; anaphylactoid reactions (see note above); pain and thrombophlebitis at injection site.

Clotrimazole

Vaginal cream: 1%; 10%.
Vaginal tablet: 100 mg; 500 mg.

Uses: anogenital candidosis; ringworm (section 13.1).

Precautions: damages latex condoms and diaphragms (advise patients to use alternative contraceptive precautions).

Dose:

Anogenital candidosis, **ADULT**, *apply* 1% cream to anogenital area 2–3 times daily.

Vaginal candidosis, **ADULT**, *vaginal administration*, (10% vaginal cream), 5 g of as a single dose at night, repeated once if necessary.

Vaginal candidosis, **ADULT**, *vaginal administration* (pessary), 100 mg at night for 6 nights or 200 mg at night for 3 nights or 500 mg at night as a single dose.

Adverse effects: local irritation.

Fluconazole

Capsule: 50 mg.
Injection: 2 mg/ml in vial.
Oral liquid: 50 mg/5 ml.

Fluconazole is a representative imidazole antifungal. Various medicines can serve as alternatives.

Uses: systemic mycoses including histoplasmosis, non-meningeal coccidioidomycosis, paracoccidioidomycosis, and blastomycosis; treatment and, in AIDS and other immunosuppressed patients, prophylaxis of cryptococcal meningitis; prevention of fungal infections in immunocompromised patients; oesophageal and oropharyngeal candidosis, vaginal candidosis and systemic candidosis; ringworm where topical treatment has failed).

Precautions: renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); monitor liver function (discontinue if signs or

symptoms of hepatic disease, especially hepatic necrosis; Appendix 5); susceptibility to QT interval prolongation; **interactions:** Appendix 1.

Dose:

Systemic mycoses, *by mouth* or *by intravenous infusion*, **ADULT,** 200 mg daily for at least 6 months; **CHILD** over 2 years, 3–6 mg/kg daily for at least 6 months.

Cryptococcal meningitis (following amphotericin B induction therapy), *by mouth* or *by intravenous infusion*, **ADULT,** 800 mg daily for 2 days, followed by 400 mg daily for 8 weeks; **CHILD,** 6–12 mg/kg daily for 8 weeks (every 72 hours in **NEONATE** up to 2 weeks old, or every 48 hours in **NEONATE** 2–4 weeks old).

Prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy, *by mouth*, **ADULT,** 200 mg daily or *by intravenous infusion*, **ADULT,** 100–200 mg daily.

Systemic candidosis (in patients unable to tolerate amphotericin B), *by mouth* or *by intravenous infusion*, **ADULT,** 400 mg as an initial dose, then 200 mg daily for at least 4 weeks; **CHILD,** 6–12 mg/kg daily (every 72 hours in **NEONATE** up to 2 weeks old, or every 48 hours in **NEONATE** 2–4 weeks old).

Oesophageal and oropharyngeal candidosis, *by mouth* or *by intravenous infusion*, **ADULT,** 200 mg as an initial dose, then 100 mg daily until symptoms resolved; up to 400 mg daily in very resistant infections; **CHILD,** 3–6 mg/kg on the first day, followed by 3 mg/kg daily (every 72 hours in **NEONATE** up to 2 weeks old, or every 48 hours in **NEONATE** 2–4 weeks old).

Vaginal candidosis, *by mouth*, **ADULT,** 150 mg as a single dose.

Prevention of fungal infections in immunocompromised patients, *by mouth* or *by intravenous infusion*, **ADULT,** 50–400 mg daily adjusted according to risk; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count is in desirable range; **CHILD,** 3–12 mg/kg daily according to extent and duration of neutropenia (every 72 hours in **NEONATE** up to 2 weeks old, or every 48 hours in **NEONATE** 2–4 weeks old); maximum, 400 mg daily.

Adverse effects: nausea, vomiting, abdominal pain, dyspepsia, flatulence, diarrhoea; headache, taste disturbances, hepatic disorders, dizziness, seizures, alopecia, pruritus; rash (withdraw treatment); angioedema, anaphylaxis, bullous lesions, toxic epidermal necrolysis, and erythema multiforme (Stevens-Johnson syndrome) reported (severe skin reactions more common in AIDS); hyperlipidaemia, leukopenia, thrombocytopenia, hypokalaemia.

Flucytosine

Capsule: 250 mg.
Infusion: 2.5 g in 250 ml.

Flucytosine is a complementary list medicine.

Uses: adjunct to amphotericin B (or fluconazole) in cryptococcal meningitis; adjunct to amphotericin B in systemic candidosis.

Precautions: the elderly; renal impairment (Appendix 4); concomitant use with amphotericin B (both nephrotoxic); liver and kidney function tests and blood counts required (monitor weekly in renal impairment or in blood disorders); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Systemic candidosis and cryptococcosis, *by intravenous infusion* (over 20–40 minutes), **ADULT** and **CHILD,** 200 mg/kg daily in 4 divided doses usually for no more than 7 days (at least 4 months in cryptococcal meningitis); reduce dose to 100–150 mg/kg daily in 4 divided doses if organisms are extremely sensitive.

Systemic candidosis, initial treatment or after intravenous therapy, *by mouth*, **ADULT** and **CHILD,** 50–150 mg/kg daily in 4 divided doses.

NOTE. For plasma concentration monitoring blood should be taken shortly before the start of the next infusion (or before the next dose by mouth); plasma concentration for optimum response, 25–50 mg/litre; plasma concentration should not be allowed to exceed 80 mg/litre.

Adverse effects: rash, nausea, vomiting and diarrhoea; alterations in liver function tests; less frequently, confusion, hallucinations, convulsions, headache, sedation, and vertigo; blood disorders including leukopenia, potentially fatal thrombocytopenia, and aplastic anaemia.

Griseofulvin

Capsule or tablet: 125 mg; 250 mg.

Uses: fungal infections of the skin, scalp, hair and nails where topical treatment has failed or is inappropriate.

Contraindications: severe liver disease (Appendix 5); pregnancy (avoid pregnancy during and for 1 month after treatment; men should not father children within 6 months of treatment; Appendix 2); porphyria; systemic lupus erythematosus (risk of exacerbation).

Precautions: pre-existing hepatic insufficiency (closely monitor hepatic function throughout treatment); blood disorders (monitor blood count

weekly during first month of treatment); breastfeeding (Appendix 3); **interactions:** Appendix 1.

SKILLED TASKS. May impair ability to perform skilled tasks, for example 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, diarrhoea, 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

Lozenge: 100 000 IU.
Pessary: 100 000 IU.
Tablet: 100 000 IU; 500 000 IU.

Uses: oral, oesophageal, intestinal, vaginal, and cutaneous candidosis.

Precautions: pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Dose:

Oral candidosis, *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 oesophageal candidosis, *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 candidosis, *vaginal administration*, **ADULT,** insert 1–2 pessaries at night for at least 2 weeks.

Adverse effects: nausea, vomiting, and diarrhoea at high doses; oral irritation and sensitization; rash and rarely erythema multiforme (Stevens-Johnson syndrome).

Potassium iodide

Saturated solution.

Potassium iodide is a complementary list medicine.

Uses: sporotrichosis; subcutaneous phycomycosis; thyrotoxicosis (section 18.8).

Contraindications: hypersensitivity to iodides; pregnancy (Appendix 2) and breastfeeding (Appendix 3); acute bronchitis or active tuberculosis.

Precautions: Addison disease; cardiac disease; hyperthyroidism; myotonia congenita; renal impairment (Appendix 4).

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: goitre, 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 diarrhoea; pulmonary oedema, bronchitis; skin reactions; depression, insomnia, impotence, and headache reported.

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, oesophagitis, and proctitis may be treated with oral aciclovir. However, HSV encephalitis or pneumonitis should be treated with intravenous aciclovir.

Valaciclovir [not included on the 15th WHO Model List], a prodrug of aciclovir, can be given by mouth as an alternative treatment for herpes simplex infections of the skin and mucous membranes (including initial and recurrent genital herpes).

Varicella–zoster infections

Chickenpox 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 chickenpox 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 which 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 [not included on the 15th WHO Model List] arrests retinochoroiditis and enteritis caused by cytomegalovirus (CMV) in HIV-infected patients. Maintenance therapy with oral ganciclovir should be given to prevent relapse of retinitis. Alternative therapy is with intravenous foscarnet [not included on the 15th WHO Model List] which can be used if necessary.

Aciclovir

Powder for injection: 250 mg (as sodium salt) in vial.
Tablet: 200 mg.

Aciclovir is a representative antiviral medicine which is active against herpes simplex virus and varicella–zoster virus. Various medicines can serve as alternatives.

Uses: treatment of primary genital herpes; disseminated varicella–zoster infections in immunocompromised patients; herpes simplex encephalitis; eye infections (section 21.1).

Precautions: maintain adequate hydration; renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Treatment of herpes simplex (including genital herpes), *by mouth*, **ADULT** and **CHILD** over 2 years, 200 mg (400 mg in the immunocompromised or if absorption is impaired) 5 times daily, usually for 5 days (longer if new

lesions appear during treatment or if healing is incomplete); **CHILD** under 2 years, half the adult dose.

Treatment of herpes simplex in the immunocompromised, severe initial genital herpes, *by intravenous infusion*, **ADULT** and **CHILD** over 12 years, 5 mg/kg every 8 hours, usually for 5 days.

Treatment of disseminated herpes simplex, *by intravenous infusion*, **NEONATE** and **INFANT** up to 3 months, 20 mg/kg every 8 hours for 10–14 days (21 days if CNS involvement); **CHILD** 3 months–12 years, 250 mg/m^2 every 8 hours, usually for 5 days.

Prevention of recurrent herpes simplex, *by mouth*, **ADULT,** 200 mg 4 times daily or 400 mg twice daily, reduced to 200 mg 2–3 times daily if possible and interrupted every 6–12 months for reassessment.

Prophylaxis of herpes simplex in the immunocompromised, *by mouth*, **ADULT** and **CHILD** over 2 years, 200–400 mg 4 times daily; **CHILD** under 2 years, half the adult dose.

Treatment of chickenpox, *by mouth*, **ADULT,** 800 mg 4–5 times daily for 5–7 days; **CHILD** under 2 years, 200 mg 4 times daily, **CHILD** 2–5 years, 400 mg 4 times daily; **CHILD** over 6 years, 800 mg 4 times daily.

Treatment of herpes zoster, *by mouth*, **ADULT,** 800 mg 5 times daily for 7–10 days.

Treatment of varicella–zoster, *by intravenous infusion*, **ADULT** and **CHILD** over 12 years, 5 mg/kg every 8 hours, usually for 5–7 days (doubled in the immunocompromised); **NEONATE** and **INFANT** up to 3 months, 10–20 mg/kg every 8 hours for at least 7 days; **CHILD** 3 months–12 years, 250 mg/m^2 every 8 hours usually for 5 days (doubled in the immunocompromised).

Treatment of herpes simplex encephalitis, varicella–zoster in the immunocompromised, *by intravenous infusion*, **ADULT** and **CHILD** over 12 years, 10 mg/kg every 8 hours; **CHILD** 3 months–12 years, 500 mg/m^2 every 8 hours; usually given for at least 10 days in encephalitis, possibly for 14–21 days.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions. In obese patients, parenteral dose should be calculated on the basis of ideal weight for height (to avoid excessive dosage).

Adverse effects: nausea, vomiting, abdominal pain, diarrhoea, headache, fatigue, rash, urticaria, pruritus, photosensitivity; very rarely hepatitis, jaundice, dyspnoea, neurological reactions (including dizziness, confusion, hallucinations, convulsions, and drowsiness), acute renal failure, anaemia, thrombocytopenia, and leukopenia; on intravenous infusion, severe local

inflammation (sometimes resulting in ulceration), and very rarely fever, agitation, tremor, and psychosis.

6.4.2 Antiretrovirals

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 its 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, to substitute for first-line regimens in cases of intolerance, or to replace failing regimens. The use of a 3- or 4-drug combination as specified in the WHO treatment guidelines 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 as a drug in its own right.

WHO has published the following guidelines on antiretroviral therapy for human immunodeficiency virus (HIV):

Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach, 2006 (available at: http://www.who.int/hiv/pub/guidelines/adult/en/index.html).

Antiretroviral therapy of HIV infection in infants and children: Towards universal access: Recommendations for a public health approach, 2006 (available at: http://www.who.int/hiv/pub/guidelines/art/en/index.html).

Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Towards universal access: Recommendations for a public health approach, 2006 (available at: http://www.who.int/hiv/pub/guidelines/pmtct/en/index.html).

Other current WHO guidelines on HIV and AIDS are available from the WHO web site: http://www.who.int/hiv/pub/guidelines/en/.

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.

Drugs used to treat HIV infection

Zidovudine, a nucleoside reverse transcriptase inhibitor (or nucleoside analogue), was the first anti-HIV drug to be introduced. Other nucleoside reverse transcriptase inhibitors include **abacavir**, **didanosine**, **emtricitabine**, **lamivudine,** and **stavudine**. Nucleotide reverse transcriptase inhibitors act in a similar way and include **tenofovir**.

The protease inhibitors include **indinavir**, **lopinavir**, **nelfinavir**, **ritonavir** and **saquinavir**. Ritonavir in low doses is used in combination with indinavir, lopinavir or saquinavir as a booster. The small amount of ritonavir in such combinations has no intrinsic antiviral activity but increases the antiviral activity of the other protease inhibitors by reducing their rate of metabolism. Indinavir, nelfinavir, ritonavir, and possibly saquinavir inhibit the cytochrome P450 enzyme system and therefore have a potential for significant drug interactions. Protease inhibitors are associated with lipodystrophy and other metabolic effects (see below).

The non-nucleoside reverse transcriptase inhibitors include **efavirenz** and **nevirapine**. They interact with a number of drugs metabolized in the liver; the doses of protease inhibitors may need to be increased when they are given with efavirenz or nevirapine. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis. Rash is also associated with efavirenz but it is usually milder. Use of efavirenz has also been associated with an increased plasma cholesterol concentration and neuropsychiatric symptoms (including sleep disorders and depression).

Initiation of treatment

The time for initiating antiviral treatment is determined by the clinical stage of the HIV infection as indicated by signs and symptoms, and where available, by the CD4-cell count.

Recommended initial treatment with a potent combination of antiretroviral medicines (highly active antiretroviral therapy or HAART) includes:

- 2 nucleoside reverse transcriptase inhibitors (section 6.4.2.1)

PLUS

- a non-nucleoside reverse transcriptase inhibitor (section 6.4.2.2)

OR

- a third nucleoside reverse transcriptase inhibitor (section 6.4.2.1)

OR

- a protease inhibitor which may be combined with ritonavir as booster (section 6.4.2.3)

Monitoring

In resource-limited settings, the basic clinical assessment before initiating antiretroviral therapy should comprise documentation of past medical history, identification of current and past HIV-related illnesses, identification of co-existing medical conditions that may influence the choice of therapy (for example, pregnancy or tuberculosis), as well as identification of current symptoms and physical signs.

The *absolute minimum laboratory tests* that should be performed before initiating antiretroviral therapy are an HIV antibody test (in patients over 18 months of age) and a haemoglobin or haematocrit measurement.

Additional basic testing should include:

- white blood cell count;
- differential cell count (to identify a decline in neturophils and the possibility of neutropenia);
- total lymphopcyte count;
- serum alanine or aspartate aminotransferase concentration to assess the possibility of hepatitis co-infection and to monitor for hepatotoxicity;
- serum creatine and/or blood urea nitrogen to assess baseline renal function;
- serum glucose;
- pregnancy tests for women.

Desirable supplemental tests include measurement of liver enzymes, creatinine, glucose, and serum lipids. CD4-cell determinations are, of course, highly desirable and efforts should be made to make these widely available. Viral load testing is currently considered to be optional because the exact threshold for

switching therapy is still not clearly defined; its role in long-term therapy, particularly in settings with a limited formulary and health-care infrastructure, is not well established.

Changing therapy

Deterioration in the patient's condition (including clinical, immunological, and virological changes) usually calls for replacement of the failing drugs. Intolerance to adverse effects and drug-induced organ dysfunction also usually require a change in therapy.

The choice of an alternative regimen depends on factors such as the response to previous treatment, tolerance, and the possibility of cross-resistance. If treatment fails, a new second-line regimen will be needed. If toxicity occurs, and it is related to an identifiable drug in the regimen, the offending drug can be substituted with another drug that does not have the same adverse effect profile. However, if it is not possible to identify the offending drug, an entirely new regimen should be considered.

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. All treatment options require careful assessment by a specialist.

A combination of **zidovudine**, **lamivudine,** and **nevirapine** is the recommended treatment for women who are pregnant and are eligible for antiviral treatment. Alternative regimens can be used. Although monotherapy with either zidovudine or nevirapine reduces transmission of infection to the neonate (see also below), a combination antiretroviral therapy not only maximizes the chance of preventing transmission but also represents optimal therapy for the mother's own health. **Low-dose ritonavir** is required if either **indinavir** or **saquinavir** is used in pregnancy because adequate drug concentration is achieved only with ritonavir boosting.

Lactic acidosis and hepatic steatosis associated with **didanosine** and **stavudine** may be more frequent in pregnant women, particularly when both drugs are used concomitantly. **Tenofovir**, despite being non-teratogenic, is associated with potential fetal bone toxicity. **Emtricitabine** is believed to be non-teratogenic in humans; however, experience of its use in pregnancy is still

limited. For these reasons it is recommended that emtricitabine, didanosine, stavudine, and tenofovir be used in pregnancy only when no alternatives are available. Protease inhibitors have been associated with glucose intolerance and pregnant women should be instructed to recognize symptoms of hyperglycaemia and to seek health care advice if these occur.

Various regimens have been used to specifically prevent the transmission of HIV from mother to the neonate at term. Women not already taking antiretrovirals should receive **zidovudine** from the 28th week of pregnancy (or as soon as possible thereafter); they should also receive a single dose of **nevirapine** during labour. Zidovudine and **lamivudine** should also be given to the mother during labour and for 1 week after birth.

Newborn infants should receive a single dose of **nevirapine**, as well as **zidovudine** for 1 week. Longer courses of zidovudine, usually up to 4 weeks, may be necessary depending on the antiretroviral medicine regimen given to the mother. Alternative regimens can be used.

Breastfeeding

Antiretroviral medicines may be present in breast milk, and may reduce the viral load in breast milk and thus reduce the risk of mother-to-child transmission through breastfeeding. However, the concentration of antiretroviral medicines in breast milk may not be adequate to prevent viral replication and there is therefore the possibility of promoting the development of drug-resistant virus which could be transmitted to the infant.

Women with HIV infection should be counselled about the risks of breastfeeding and advised, if it is possible, to avoid breastfeeding. When replacement feeding is acceptable, feasible, affordable, sustainable, and safe, breastfeeding should be avoided. Otherwise, exclusive breastfeeding is recommended during the first months of life and should then be discontinued as soon as it is feasible. HIV-infected women should be counselled on infant feeding options and should be supported in their choice.

Post-exposure prophylaxis

Treatment with antiretroviral medicines may be appropriate following occupational exposure to HIV-contaminated material and sexual assault. Immediate expert advice should be sought in such cases; national guidelines on post-exposure prophylaxis for health-care workers and victims of sexual assault have been developed and local ones may also be available.

Lipodystrophy and metabolic effects

Metabolic effects associated with antiretroviral therapy include fat redistribution, insulin resistance and dyslipidaemia; collectively these effects

have been termed *lipodystrophy syndrome*. Regimens containing protease inhibitors and some nucleoside reverse transcriptase inhibitors (particularly stavudine) are associated with redistribution of body fat in some patients (for example, decreased fat under the skin, increased abdominal fat, "buffalo humps" and breast enlargement). Some antiretrovirals, particularly the protease inhibitors, are associated with dyslipidaemia. Protease inhibitors are also associated with metabolic abnormalities such as insulin resistance and hyperglycaemia. Clinical examination should include an evaluation of fat distribution; monitoring of serum lipids and blood glucose should also be considered.

Abbreviations

The following table lists the abbreviations that are sometimes used for antiretroviral medicines.

Generic name	Most common and preferred abbreviation	Alternative abbreviations
Abacavir	ABC	ABV
Atazanavir	ATV	ATZ
Darunavir	DRV	TMC-114, DAR
Didanosine	ddI	DDI, DID
Efavirenz	EFV	EFZ
Emtricitabine	FTC	ETC, ETB
Enfuvirtide	ENF	T-20, ENV, EFT
Fosamprenavir	FPV	f-APV, FOS
Indinavir	IDV	IND
Lamivudine	3TC	LMV, LAM
Lopinavir	LPV	LOP
Maraviroc	MVC	UK-427,857, MRV, MAR
Nevirapine	NVP	NEV
Raltegravir	RAL	MK-0518, RTG, RGV, RALT
Ritonavir	RTV, r*	RIT
Saquinavir	SQV	SAQ
Stavudine	d4T	STV, D4T
Tenofovir	TDF	TNV, TNF
Tipranavir	TPV	PNU-140,690, TPN
Zidovudine	AZT	ZDV

* Preferred option if used at low dose as a pharmacological booster.

Fixed-dose combinations

Efavirenz + emtricitabine + tenofovir

Tablet: 600 mg + 200 mg + 300 mg.

Uses: HIV infection alone as a complete regimen or in combination with other antiretroviral medicines.

Contraindications: pregnancy (see introductory note above and under Efavirenz; Appendix 2).

Precautions: see under Efavirenz, Emtricitabine, and 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.

Adverse effects: see under Efavirenz, Emtricitabine, and Tenofovir.

Emtricitabine + tenofovir

Tablet: 200 mg + 300 mg.

Uses: HIV infection alone as a complete regimen or in combination with other antiretroviral medicines.

Precautions: see under Emtricitabine and 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 and Tenofovir.

Stavudine + lamivudine + nevirapine

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, and 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, and Stavudine.

Zidovudine + lamivudine

Tablet: 300 mg + 150 mg.

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 one other antiretroviral medicine.

Precautions: see under Lamivudine, and Zidovudine.

Dose:

HIV infection in combination with at least one other antiretroviral medicine, *by mouth*, **ADULT** and **CHILD** over 12 years, 1 tablet twice daily.

Adverse effects: see under Lamivudine and Zidovudine.

Zidovudine + lamivudine + nevirapine

Tablet: 300 mg + 150 mg + 200 mg.

NOTE. The abbreviation, AZT, which has sometimes been used for zidovudine has also been used for another medicine.

Uses: HIV infection alone as a complete regimen or in combination with other antiretroviral medicines.

Precautions: see under Lamivudine, Nevirapine, and Zidovudine.

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 of 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, and Zidovudine.

6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

In some settings, it may not be possible to carry out full monitoring as described under each drug entry; in such cases the level of monitoring should be determined by local guidelines (see also introductory note above).

Abacavir

Oral liquid: 100 mg (as sulfate)/5 ml.
Tablet: 300 mg (as sulfate).

Uses: HIV infection in combination with at least two other antiretroviral medicines.

Precautions: chronic hepatitis B or C, hepatic impairment (see Note on hepatic disease below; Appendix 5); renal impairment (Appendix 4); pregnancy (see introductory note above; Appendix 2) and breastfeeding (see introductory note above; Appendix 3); **interactions**: Appendix 1.

HYPERSENSITIVITY Reactions. Life-threatening hypersensitivity reactions characterized most commonly by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, dyspnoea, cough, lethargy, malaise, headache, and myalgia, less frequently by mouth ulceration, oedema, hypotension, sore throat, adult respiratory distress syndrome, paraesthesia, 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 which 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 hyperlactataemia, progressive hepatomegaly, or lactic acidosis occurs.

Dose:

HIV infection in combination with at least two other antiretroviral medicines, *by mouth*, **ADULT,** 300 mg twice daily; **CHILD** 3 months–16 years, 8 mg/kg twice daily (maximum, 600 mg daily).

Adverse effects: hypersensitivity reactions including nausea, vomiting, diarrhoea, 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.

Didanosine

Buffered powder for oral liquid: 100 mg; 167 mg; 250 mg packets.
Capsule (unbuffered enteric-coated):125 mg; 200 mg; 250 mg; 400 mg.
Tablet (buffered chewable, dispersible): 25 mg; 50 mg; 100 mg; 150 mg; 200 mg.

NOTE. Antacids in some formulations may affect absorption of other drugs (see also Appendix 1).

Uses: HIV infection in combination with at least two other antiretroviral medicines.

Precautions: history of pancreatitis (preferably avoid, otherwise exercise extreme caution; see also note below); peripheral neuropathy or hyperuricaemia (see also under Adverse effects); chronic hepatitis B or C; renal impairment (Appendix 4); hepatic impairment (see note on Hepatic diseases below; Appendix 5); pregnancy (see introductory note above; Appendix 2); breastfeeding (see introductory note above; Appendix 3); dilated retinal examinations recommended (especially in children) every 6 months, or if visual changes occur; **interactions:** Appendix 1.

PANCREATITIS. If symptoms of pancreatitis develop or if serum amylase or lipase is raised (even if patient is asymptomatic), suspend treatment until diagnosis of pancreatitis is excluded; on return to normal values, re-initiate treatment only if essential (using a low dose, increased gradually if appropriate). Whenever possible avoid concomitant treatment with other drugs known to cause pancreatic toxicity (for example, intravenous pentamidine); monitor patient closely if concomitant therapy is unavoidable. Since significant elevations of triglycerides cause pancreatitis, monitor patient closely if these are elevated.

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 hyperlactataemia, progressive hepatomegaly or lactic acidosis occurs.

Dose:

In combination with other antiretroviral medicines, *by mouth*, **ADULT** under 60 kg, 250 mg daily in 1–2 divided doses; **ADULT** over 60 kg, 400 mg daily in 1–2 divided doses; **CHILD** under 3 months, 50 mg/m^2 twice daily; **CHILD** 3 months–13 years, 90–120 mg/m^2 twice daily or 180-240 mg/m^2 once daily.

PATIENT ADVICE. To ensure sufficient antacid from buffered tablets, each dose to be taken as 2 tablets (child under 1 year, 1 tablet), chewed thoroughly, crushed, or dispersed in water; tablets should be taken at least 1 hour before food or on an empty stomach.

Adverse effects: pancreatitis (see also under Precautions); peripheral neuropathy especially in advanced HIV infection (suspend treatment; a reduced dose may be tolerated when symptoms resolve); hyperuricaemia (suspend treatment if significant elevation); diarrhoea (occasionally serious); nausea, vomiting, dry mouth, parotid gland enlargement, sialadenitis, headache, hypersensitivity reactions, dry eyes, retinal and optic nerve changes (especially in children), diabetes mellitus, hypoglycaemia, raised liver enzymes (see also under Precautions), liver failure, acute renal failure, and rhabdomyolysis also reported; alopecia, insomnia, dizziness, blood disorders, lipodystrophy (see introductory note above).

Emtricitabine

Capsule: 200 mg.
Oral liquid: 10 mg/ml.

NOTE. 240 mg oral solution or 200 mg capsule. 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 two other antiretroviral medicines.

Precautions: renal impairment (Appendix 4), hepatic disease (see note below); pregnancy (see introductory note above; Appendix 2) and breastfeeding (see introductory note above; Appendix 3), **interactions:** Appendix 1.

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 hyperlactataemia, progressive hepatomegaly or lactic acidosis occurs. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of emtricitabine.

Dose:

HIV infection (in combination with other antiretroviral medicines), *by mouth*, **ADULT** and **CHILD**, over 33 kg, 1 capsule (200 mg) or 24 ml (240 mg) oral solution once daily; **CHILD** 4 months–18 years, under 33 kg, 6 mg/kg oral solution once daily.

Adverse effects: nausea, vomiting, abdominal pain, dyspepsia, diarrhoea; headache, dizziness, peripheral neuropathy, asthenia, insomnia, abnormal dreams, depression; anaemia, neutropenia; arthralgia, myalgia, bone necrosis; raised serum lipase, amylase, creatine kinase, and liver enzymes (see also note on Hepatic disease above), hyperbilirubinaemia, hypertriglyceridaemia, hyperglycaemia; rash, pruritus, urticaria, hyperpigmentation; lipodystrophy and metabolic effects (see also introductory note above).

Lamivudine

Oral liquid: 50 mg/5 ml.
Tablet: 150 mg.

Uses: HIV infection in combination with at least 2 other antiretroviral medicines; prevention of mother-to-child HIV transmission.

Precautions: renal impairment (Appendix 4); chronic hepatitis B or C; hepatic disease (see note below); pregnancy (see introductory note above; Appendix 2); breastfeeding (see introductory note above; Appendix 3); **interactions:** Appendix 1.

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 hyperlactataemia, 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 (maximum, 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 labour followed by 150 mg every 12 hours until delivery; after delivery 150 mg twice a day for 7 days.

Adverse effects: nausea, vomiting, diarrhoea, abdominal pain; cough; headache, fatigue, insomnia; malaise, fever, rash, alopecia, muscle disorders; nasal symptoms; peripheral neuropathy reported; rarely pancreatitis (discontinue); neutropenia, anaemia, thrombocytopenia and red cell aplasia; lactic acidosis; raised liver enzymes and serum amylase reported.

Stavudine

Capsule: 15 mg; 20 mg; 30 mg; 40 mg.
Powder for oral liquid: 5 mg/5 ml.

Uses: HIV infection in combination with at least two other antiretroviral medicines.

Precautions: history of peripheral neuropathy (see note below); history of pancreatitis or concomitant use with other drugs associated with pancreatitis; chronic hepatitis B or C; hepatic disease (see note below); renal impairment (Appendix 4); pregnancy (see introductory note above; Appendix 2); breastfeeding (see introductory note above; Appendix 3); **interactions:** Appendix 1.

PERIPHERAL NEUROPATHY. Suspend if peripheral neuropathy develops (characterized by persistent numbness, tingling or pain in the feet or hands); if symptoms resolve satisfactorily on withdrawal, and if stavudine needs to be continued, resume treatment at half the previous dose.

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 hyperlactataemia, progressive hepatomegaly, or lactic acidosis occurs.

Dose:

HIV infection (in combination with other antiretroviral medicines), *by mouth*, **ADULT** under 60 kg, 30 mg twice daily preferably at least 1 hour before food; **ADULT** over 60 kg, 40 mg twice daily; **CHILD** over 3 months, under 30 kg, 1 mg/kg twice daily; **CHILD** over 30 kg, 30 mg twice daily.

Adverse effects: peripheral neuropathy (dose-related; see note above); pancreatitis; nausea, vomiting, diarrhoea, constipation, anorexia, abdominal discomfort; chest pain; dyspnoea; headache, dizziness, insomnia, mood changes; abnormal dreams, cognitive dysfunction, drowsiness, depression, anxiety; gynaecomastia; asthenia, musculoskeletal pain; influenza-like symptoms, rash and other allergic reactions; lymphadenopathy; neoplasms; elevated liver enzymes (see note on Hepatic disease above) and serum amylase; neutropenia, thrombocytopenia.

Tenofovir disoproxil fumarate

Tablet: 300 mg (tenofovir disoproxil fumarate - equivalent to 245 mg tenofovir disoproxil).

Uses: HIV infection in combination with other antiretroviral medicines.

Precautions: renal impairment (Appendix 4), hepatic disease (see note below); pregnancy (see introductory note above; Appendix 2); breastfeeding (see introductory note above; Appendix 3); **interactions:** Appendix 1.

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 hyperlactataemia, 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,** 245 mg (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, diarrhoea, anorexia; hypophosphataemia; dizziness, peripheral neuropathy, headache, dyspnoea, insomnia, depression, asthenia, sweating, myalgia, rash, hypertriglyceridaemia, hyperglycaemia, neutropenia; nephritis, nephrogenic diabetes insipidus, renal impairment, effects on renal proximal tubules (including Fanconi syndrome), proteinuria, polyuria; reduced bone density; pancreatitis, hepatitis, lactic acidosis; raised liver enzymes, creatinine, and serum amylase reported (see also note on Hepatic disease above).

Zidovudine

Capsule: 100 mg; 250 mg.
Oral liquid: 50 mg/5 ml.
Solution for IV infusion injection: 10 mg/ml in 20-ml vial.
Tablet: 300 mg.

Also known as azidothymidine.

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 haemoglobin (consult product literature); neonates with either hyperbilirubinaemia requiring treatment other than phototherapy or raised transaminase (consult product literature).

Precautions: haematological toxicity; vitamin B_{12} deficiency (increased risk of neutropenia); anaemia or myelosuppression (reduce dose or interrupt treatment according to product literature); renal impairment (Appendix 4); chronic hepatitis B or C; hepatic impairment (see note on Hepatic disease below; Appendix 5); the elderly; pregnancy (see introductory note above; Appendix 2); breastfeeding (see introductory note above; Appendix 3); **interactions:** Appendix 1.

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 hyperlactataemia, 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/m^2 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/m^2 every 6 hours (120 mg/m^2 every 6 hours approximates to 180 mg/m^2 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 labour (or 300 mg at onset of labour, 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;

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: anaemia (may require transfusion), neutropenia, and leukopenia (all more frequent with high dose and advanced disease); also nausea and vomiting, abdominal pain, dyspepsia, diarrhoea, flatulence, taste disturbance, pancreatitis, liver disorders including fatty change and raised

bilirubin and liver enzymes (see note on Hepatic disease above); chest pain, dyspnoea, cough; influenza-like symptoms, headache, fever, paraesthesia, neuropathy, convulsions, dizziness, somnolence, insomnia, anxiety, depression, loss of mental acuity, malaise, anorexia, asthenia, myopathy, myalgia; pancytopenia, thrombocytopenia; gynaecomastia; urinary frequency; rash, pruritus; pigmentation of nail, skin, and oral mucosa.

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

In some settings, it may not be possible to carry out full monitoring as described under each drug entry; in such cases, the level of monitoring should be determined by local guidelines (see also introductory note above).

Efavirenz

Capsule: 50 mg; 100 mg; 200 mg.
Oral liquid: 150 mg/5 ml.
Tablet: 600 mg.

NOTE. The bioavailability of efavirenz from the oral solution is lower than that from the capsules and tablets; the oral solution is therefore not interchangeable with either the capsules or tablets on a milligram-for-milligram basis.

Uses: HIV infection in combination with at least two other antiretroviral medicines.

Contraindications: pregnancy (see introductory note above; Appendix 2; substitute nevirapine for efavirenz in pregnant women or women for whom effective contraception cannot be assured).

Precautions: chronic hepatitis B or C; hepatic impairment (avoid if severe; Appendix 5); severe renal impairment (Appendix 4); breastfeeding (see introductory note above; Appendix 3); the elderly; history of mental illness or seizures; **interactions:** Appendix 1.

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 occur.

Dose:

HIV infection (in combination with other antiretroviral medicines),

by mouth (as tablets or capsules), **ADULT** and **CHILD** 40 kg and over, 600 mg once daily; **CHILD** over 3 years/10–14 kg, 200 mg once daily; **CHILD** 15–19 kg, 250 mg once daily; **CHILD** 20–24 kg, 300 mg once daily; **CHILD** 25–32 kg, 350 mg once daily; **CHILD** 33–39 kg, 400 mg once daily;

by mouth (as oral solution), **ADULT** and **CHILD** 40 kg and over, 720 mg once daily; **CHILD** over 3 years/10–15 kg, 270 mg once daily; **CHILD** 15–20 kg, 300 mg once daily; **CHILD** 20–24 kg, 360 mg once daily; **CHILD** 25–32 kg, 450 mg once daily; **CHILD** 33–39 kg, 510 mg once daily.

Adverse effects: rash including Stevens-Johnson syndrome (see also note above); abdominal pain, diarrhoea, 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 (especially if seropositive for hepatitis B or C), pancreatitis, gynaecomastia, and photosensitivity also reported.

Nevirapine

Oral liquid: 50 mg/5 ml.
Tablet: 200 mg.

Uses: HIV infection in combination with at least two other antiretroviral medicines; prevention of mother-to-child HIV transmission.

Contraindications: severe hepatic impairment; post-exposure prophylaxis

Precautions: hepatic impairment (see note below; Appendix 5); 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/mm^3 and in men with a CD4 cell count greater than 400 cells/mm^3; pregnancy (see introductory note above; Appendix 2); breastfeeding (see introductory note above; Appendix 3); **interactions:** Appendix 1.

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.

NOTE. If treatment is interrupted for more than 7 days, reintroduce at a low dose and increase dose cautiously.

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 oedema, general malaise, or hypersensitivity reactions; if rash is mild or moderate, continue without interruption but dose should not be increased until rash resolves

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/m^2 twice daily for 14 days, then 200 mg/m^2 twice daily; **CHILD** 1 month–13 years, 120 mg/m^2 once daily for first 14 days, then (if no rash present) 120–200 mg/m^2 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 labour; **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/m^2) and increase dose cautiously.

Adverse effects: rash including Stevens-Johnson syndrome and rarely, toxic epidermal necrolysis (see also note on Rash above); nausea, hepatitis (see also note on Hepatic disease above), headache; less commonly vomiting, abdominal pain, fatigue, fever, and myalgia; rarely diarrhoea, angioedema, anaphylaxis, hypersensitivity reactions (may involve hepatic reactions and rash; see note on Hepatic disease above); arthralgia, anaemia, and granulocytopenia (more frequent in children); very rarely neuropsychiatric reactions.

6.4.2.3 Protease inhibitors

In some settings, it may not be possible to carry out full monitoring as described under each drug entry; in such cases, the level of monitoring should be determined by local guidelines (see also introductory note above).

Indinavir

Capsule: 200 mg; 333 mg; 400 mg (as sulfate).

Uses: HIV infection usually in combination with two nucleoside reverse transcriptase inhibitors and a low-dose ritonavir booster.

Contraindications: porphyria.

Precautions: chronic hepatitis B or C (increased risk of hepatotoxicity); hepatic impairment (Appendix 5); 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); haemophilia; pregnancy (see introductory note above; Appendix 2); breastfeeding (see introductory note above; Appendix 3); metabolism of many drugs inhibited if administered concomitantly; **interactions:** Appendix 1.

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/m^2 every 8 hours (maximum, 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, diarrhoea, abdominal discomfort, dyspepsia, flatulence, pancreatitis, dry mouth, taste disturbances; headache, dizziness, insomnia; myalgia, myositis, rhabdomyolysis, fatigue, hypoaesthesia, paraesthesia; hyperglycaemia; hypersensitivity reactions, rash (including Stevens-Johnson syndrome), pruritus, dry skin, hyperpigmentation, alopecia, paronychia; interstital nephritis, nephrolithiasis (may require interruption or discontinuation; more frequent in children), dysuria, haematuria, crystalluria, proteinuria, pyuria (in children); hepatitis, transient hyperbilirubinaemia;

blood disorders including neutropenia, and haemolytic anaemia; lipodystrophy and metabolic effects (see also introductory note above).

Lopinavir + ritonavir

Capsule: 133.3 mg + 33.3 mg.
Oral liquid: 400 mg + 100 mg/5 ml.

NOTE. 5 ml oral solution = 3 capsules; 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 (see also introductory note above under Drugs used to treat HIV infection); 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 5); renal impairment (Appendix 4); haemophilia; pregnancy (see introductory note above; Appendix 2) and breastfeeding (see introductory note above; Appendix 3); 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 1.

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 m^2 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/m^2 + ritonavir, 56.25 mg/m^2 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 anaemia, neutropenia, and thrombocytopenia), sleep disturbances, fatigue, headache, dizziness, paraesthesia; myalgia, myositis, rhabdomyolysis; taste disturbances;

rash, pruritus, Stevens-Johnson syndrome, hypersensitivity reactions; lipodystophy 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, oedema, dyspnoea, 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, hyperuricaemia, 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

Oral powder: 50 mg/g.
Tablet: 250 mg (as mesilate).

Uses: HIV infection in combination with at least two other antiretroviral medicines.

Precautions: renal impairment (Appendix 5); hepatic impairment, chronic hepatitis B or C (increased risk of hepatotoxicity); diabetes mellitus; haemophilia; pregnancy (see introductory note above; Appendix 2); breastfeeding (see introductory note above; Appendix 3); **interactions:** Appendix 1.

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: diarrhoea, 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 oedema); myalgia, myositis and rhabdomyolysis; lipodystrophy and metabolic effects (see also introductory note above).

Ritonavir

Oral liquid: 400 mg/5 ml.
Oral solid dosage form: 100 mg.

Uses: HIV infection, as a booster to increase the effect of indinavir, lopinavir or saquinavir, in combination with at least two other antiretroviral medicines.

Contraindications: severe hepatic impairment; porphyria.

Precautions: chronic hepatitis B or C (increased risk of hepatotoxicity); hepatic impairment (Appendix 5); diabetes mellitus; haemophilia; pregnancy (see introductory note above; Appendix 2); breastfeeding (see introductory note above; Appendix 3); **interactions:** Appendix 1.

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/m^2 twice daily or
3–5 mg/kg twice daily (maximum, 100 mg twice daily).

Adverse effects: nausea, vomiting, diarrhoea (may impair absorption — close monitoring required), abdominal pain, taste disturbances, dyspepsia, anorexia, throat irritation; vasodilatation, hypotension, syncope; headache, drowsiness; circumoral and peripheral paraesthesia, hyperaesthesia, dizziness, sleep disturbances, fatigue, rash, hypersensitivity reactions, leukopenia; seizures; raised liver enzymes, bilirubin, and uric acid; occasionally flatulence, eructation, dry mouth and ulceration, cough, anxiety, fever, pain, menorrhagia, myalgia, myositis, rhabdomyolysis, weight loss, decreased thyroxine, sweating, pruritus, electrolyte disturbances, anaemia, neutropenia, and increased prothrombin time; pancreatitis (see also note on Pancreatitis, above); lipodystrophy and metabolic effects (see also introductory note above).

Saquinavir

Capsule: 200 mg.

Uses: HIV infection in combination with at least two other antiretroviral medicines and usually a low-dose ritonavir booster.

Contraindications: severe hepatic impairment (Appendix 5).

Precautions: chronic hepatitis B or C; hepatic impairment (Appendix 5); renal impairment (Appendix 4); diabetes mellitus; haemophilia; pregnancy (see introductory note above; Appendix 2); breastfeeding (see introductory note

above; Appendix 3); concomitant use of garlic (reduces plasma saquinavir concentration); **interactions:** Appendix 1.

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. Administer with or after food.

NOTE. To avoid confusion between the different formulations of saquinavir, prescribers should specify the brand to be dispensed; absorption from gel-filled capsules containing saquinavir is much greater than from capsules containing saquinavir mesilate. Treatment should generally be initiated with gel-filled capsules.

Adverse effects: diarrhoea, buccal and mucosal ulceration, abdominal discomfort, nausea, vomiting, taste disturbances; headache, chest pain, peripheral neuropathy, paraesthesia, 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).

6.4.3 Other antivirals

Ribavirin

Injection for intravenous administration: 1000 mg and 800 mg in 10-ml phosphate buffer solution.
Oral solid dosage forms: 200 mg; 400 mg; 600 mg.

Also known as Tribavirin.

HAEMORRHAGIC FEVER VIRUS INFECTION. Ribavirin inhibits a variety of DNA and RNA viruses. It is active against viral haemorrhagic fevers caused by the *Arenaviridae* and *Bunyaviridae* family viruses, which include Lassa fever, Argentine haemorrhagic fever, Crimean–Congo haemorrhagic fever, and haemorrhagic fever with renal syndrome. Treatment of Lassa fever is most effective if started within 6 days of the onset of fever.

Other indications for ribavirin include the treatment of respiratory syncytial virus infection, and, with peginterferon alfa or interferon alfa [not included on the 15th

WHO Model List] for the treatment of chronic hepatitis C infection (consult manufacturer's literature for details).

Uses: treatment of haemorrhagic fever, including Lassa fever, Argentine haemorrhagic fever, and Crimean–Congo haemorrhagic fever; haemorrhagic fever with renal syndrome.

Contraindications: pregnancy (see note below and under Precautions; Appendix 2); breastfeeding (Appendix 3); severe cardiac disease (including unstable or uncontrolled cardiac disease in previous 6 months); haemoglobinopathies (including thalassemia or sickle-cell anaemia), haemoglobin levels less than 8 g/dl; severe debilitating medical conditions; severe hepatic dysfunction or decompensated cirrhosis of the liver (Appendix 5); autoimmune disease (including autoimmune hepatitis).

PREGNANCY. Risk of serious fetal abnormalities exists when ribavirin is used during pregnancy, but because of the high risk of mortality from haemorrhagic fevers, for both the mother and the fetus, maternal benefit should be considered. Lassa fever is especially severe late in pregnancy, with maternal death or fetal loss occurring in more than 80% of cases during the third trimester.

Precautions: renal impairment (Appendix 4); monitor blood counts at least weekly; **interactions:** Appendix 1.

NOTE. Both men and women should be advised to use contraception during and for at least 7 months after treatment.

Dose:

Haemorrhagic fevers, *by mouth*, **ADULT,** initially 2 g then 1 g every 6 hours for 4 days, then 500 mg every 6 hours for 6 days; **CHILD,** initially 30 mg/kg then 15 mg/kg every 6 hours for 4 days, then 7 mg/kg every 6 hours for 6 days.

PATIENT ADVICE. Oral ribavirin should be taken with food.

Haemorrhagic fevers, *by slow intravenous infusion* (over 10–15 minutes), **ADULT,** initially 17 mg/kg (maximum, 1 g) then 17 mg/kg every 6 hours for 4 days, then 8 mg/kg (maximum, 500 mg) every 8 hours for 6 days; **CHILD,** initially 17 mg/kg, then 17 mg/kg every 6 hours for 4 days, then 7 mg/kg every 8 hours for 6 days.

Haemorrhagic fever with renal syndrome, *by slow intravenous infusion* (over 10–15 minutes), **ADULT,** initially 33 mg/kg (maximum, 1 g), then 16 mg/kg (maximum, 1 g) every 6 hours for 4 days, then 8 mg/kg (maximum, 500 mg) every 8 hours for 6 days.

Adverse effects: haemolytic anaemia, neutropenia, thrombocytopenia, aplastic anaemia; myocardial infarction, arrhythmias; infections; nausea, vomiting, diarrhoea, colitis, anorexia, fever, rigors, dyspnoea, cough, dizziness, insomnia, myalgia, arthralgia, fatigue, headache, impaired concentration, irritability, anxiety, depression, suicidal ideation (more frequent in children),

autoimmune disorders, pulmonary toxicity, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism; retinal haemorrhage, retinal thrombosis; alopecia, pruritus, rash; rarely hypersensitivity reactions.

6.5 Antiprotozoal medicines

6.5.1 Antiamoebic and antigiardiasis medicines

Amoebiasis

Amoebic dysentery is caused by *Entamoeba histolytica*. It is transmitted by the faeco-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 amoebicide which will reduce the risk of transmission and protect the patient from invasive amoebiasis. **Diloxanide** is most widely used, but other compounds, including clefamide, etofamide, and teclozan [none of which are included on the 15th WHO Model List], are also effective. 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) amoebiasis may be classified as either intestinal or extra-intestinal. Intestinal forms of amoebiasis include amoebic dysentery and non-dysenteric amoebic colitis. Extra-intestinal amoebiasis most commonly involves the liver, but in some cases may involve the skin, the genitourinary tract, the lung and the brain. Invasive amoebiasis is more likely in malnutrition, immunosuppression, and pregnancy. Amoebic dysentery may take a fulminating course in late pregnancy and the puerperium period; treatment with **metronidazole** may be life saving. In less severe infection, metronidazole should, if possible, be avoided in the first trimester. All patients with invasive amoebiasis require treatment with a systemically active compound such as **metronidazole**, ornidazole or tinidazole [neither ornidazole or tinidazole are included on the 15th WHO Model List] followed by a luminal amoebicide (such as diloxanide) in order to eliminate any surviving organisms in the colon. Combined preparations are useful.

In severe cases of amoebic dysentery, tetracycline given in combination with a systemic amoebicide 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.

Diloxanide

Tablet: 500 mg (furoate).

Uses: amoebiasis (asymptomatic carriers in non-endemic areas; eradication of residual luminal amoebae after treatment of invasive disease with other medicines).

Precautions: pregnancy (defer treatment until after first trimester; Appendix 2) and breastfeeding (Appendix 3).

Dose:

Amoebiasis (see Uses above), *by mouth*, **ADULT,** 500 mg 3 times daily for 10 days; **CHILD** over 25 kg, 20 mg/kg daily in 3 divided doses for 10 days; course may be repeated if necessary.

Adverse effects: flatulence; occasionally, vomiting, pruritus, and urticaria.

Metronidazole

Injection: 500 mg in 100-ml vial.
Oral liquid: 200 mg (as benzoate)/5 ml.
Tablet: 200–500 mg.

Metronidazole is a representative antibacterial and antiprotozoal agent. Various medicines can serve as alternatives.

Uses: invasive amoebiasis and giardiasis; trichomoniasis; tissue nematode infections especially dracunculiasis (section 6.1.1); bacterial infections (section 6.2.2); *Helicobacter pylori* eradication (section 17.1).

Contraindications: chronic alcohol dependence.

Precautions: disulfiram-like reaction with alcohol; hepatic impairment and hepatic encephalopathy (Appendix 5); pregnancy (see introductory note above; Appendix 2); breastfeeding (Appendix 3); clinical and laboratory monitoring recommended in courses lasting longer than 10 days; **interactions:** Appendix 1.

Dose:

Invasive amoebiasis, *by mouth*, **ADULT** and **CHILD,** 30 mg/kg daily in 3 divided doses for 8–10 days; followed by a course of a luminal amoebicide (see introductory note above).

Invasive amoebiasis (if oral administration not possible), *by intravenous infusion*, **ADULT** and **CHILD,** 30 mg/kg daily in 3 divided doses (until patient able to complete course with oral drugs); subsequent course of luminal amoebicide (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 amoebiasis and giardiasis, various dosage regimens are used and definitive recommendations should be based on local experience.

PATIENT ADVICE. Metronidazole tablets should be swallowed whole with water, during or after a meal; the oral suspension should be taken 1 hour before a meal.

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.

6.5.2 Antileishmaniasis medicines

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 (visceral leishmaniasis in south Asia and in eastern Africa, and cutaneous leishmaniasis caused by *Leishmania tropica*), human beings are the

incidental hosts of infection, and mammals, such as rodents and canids, are the reservoir hosts. The parasites are transmitted by sandflies.

Visceral leishmaniasis

Visceral leishmaniasis (kala-azar) is caused by *Leishmania donovani* and *L. infantum* (Old World) and by *L. chagasi* (New World). It is usually responsive, at least initially, to the pentavalent antimony compounds, meglumine antimoniate or sodium stibogluconate [not included on the 15th WHO Model List]. Patients are considered to be parasitologically cured when no parasites are detected in splenic or bone marrow aspirates. **Amphotericin B,** miltefosine or a combination of an antimonial with either miltefosine, **amphotericin B**, **paromomycin** (aminosidine), or **pentamidine,** have been used with success in patients in relapse who have become unresponsive to antimonials alone.

In some areas, resistance to antimonials is widespread (for example, in India). In these areas, amphotericin B, parenteral **paromomycin** (aminosidine), or oral miltefosine [not included on the 15th WHO Model List], can be used for the treatment of visceral leishmaniasis.

Cutaneous leishmaniasis

Cutaneous leishmaniasis comprises 2 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. Infections due to *L. braziliensis* and the less common, *L. panamensis,* should be treated with systemic **antimonials** because of the risk of mucosal involvement. At conventional doses *L. aethiopica* is less responsive and the sores should be left to heal spontaneously if there is no evidence of diffuse cutaneous involvement. *L. guyanensis* infections should be treated with **pentamidine**.

Mucocutaneous leishmaniasis

Mucocutaneous leishmaniasis is caused by *L. braziliensis* or *L. panamensis*. In this form of the disease, the primary lesions do not heal and spread to the mucosa may occur. It usually responds to **antimonials** and, when relapses occur, further extended courses of treatment are often successful. Patients who still fail to respond should receive **amphotericin B** or **pentamidine**, although neither treatment is highly satisfactory. Because of resistance to antimonials, *L. aethiopica* infections should be treated with pentamidine from the outset until complete healing occurs.

Emergency use of corticosteroids may be needed to control pharyngeal or tracheal oedema produced by severe inflammation resulting from antigens liberated from dead parasites during the early phase of treatment.

Antibiotics may also be needed to treat secondary infections. Plastic surgery offers the only means of ameliorating disfiguring scars.

Diffuse cutaneous leishmaniasis

Diffuse cutaneous leishmaniasis usually occurs following infection with *L. amazonensis, L. aethiopica,* or *L. mexicana* and is usually treated with **antimonial compounds**, but relapses must be expected and repeated courses of **pentamidine** may be needed until clinical immunity is established.

Amphotericin B

Powder for injection: 50 mg in vial.

Amphotericin B is a complementary list medicine for the treatment of leishmaniasis.

Uses: visceral and mucocutaneous leishmaniasis unresponsive to antimonial compounds; fungal infections (section 6.3).

Precautions: initial test dose required (risk of anaphylaxis; see note below); renal impairment (Appendix 4); monitor hepatic and renal function; blood counts, and plasma electrolyte concentrations throughout treatment; concomitant use of corticosteroids (avoid except to control inflammatory reactions); pregnancy (Appendix 2) and breastfeeding (Appendix 3); avoid rapid infusion (risk of arrhythmias); **interactions:** Appendix 1.

ANAPHYLAXIS. Anaphylaxis rarely occurs with intravenous amphotericin B and a test dose is advisable before commencing the first infusion. The patient should be observed for about 30 minutes after the test dose.

Dose:

Visceral and mucocutaneous leishmaniasis (unresponsive to antimonial compounds), *by intravenous infusion*, **ADULT,** initial test dose, 1 mg over 20–30 minutes, followed by 5–10 mg, gradually increased by 5–10 mg daily

up to 0.5–1 mg/kg daily, which is then administered on alternate days (a total cumulative dose of 1–3 g is usually required).

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: fever, headache, anorexia, weight loss, nausea and vomiting, malaise, diarrhoea, muscle and joint pain, dyspepsia, epigastric pain; renal function disturbances including hypokalaemia, hypomagnesaemia, and renal toxicity; blood disorders; cardiovascular toxicity (including arrhythmias); neurological disorders (including peripheral neuropathy); abnormal liver function (discontinue treatment); rash; anaphylactoid reactions (see note under Precautions above); pain and thrombophlebitis at injection site.

Meglumine antimoniate

Injection: 30%, equivalent to approximately 8.1% antimony in 5-ml ampoule.

Meglumine antimoniate and sodium stibogluconate are the pentavalent antimony compound used to treat leishmaniasis.

Uses: leishmaniasis.

Contraindications: severe cardiac, liver, and kidney disorders; breastfeeding (Appendix 3).

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 4 and 5); 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 (see also introductory notes above, under Mucocutaneous disease).

Dose:

NOTE. Doses are expressed in terms of pentavalent antimony.

Visceral leishmaniasis, *by intramuscular injection*, **ADULT** and **CHILD,** 20 mg/kg daily 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; if no apparent response, may be repeated once or twice at intervals of 1–2 days; relapse is unusual.

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
- Super-infected lesions
- Lesions produced by *L. brazilensis, L. guyanensis* and *L. tropica.*

When systemic treatment is required for cutaneous leishmaniasis (except for lesions produced by *L. brazilensis, L. guyanensis* and *L. tropica*), pentavalent antimonials *by intramuscular injection* could be used with the following doses: **ADULT** and **CHILD,** 10–20 mg/kg daily until a few days after clinical cure and negative slit-skin smear. The treatment of cutaneous leishmaniasis by *L. braziliensis* requires 20 mg/kg daily, until lesion has healed and for at least 4 weeks; relapse may occur due to inadequate dosage or interrupted treatment; relapse after full course of treatment requires treatment with pentamidine (see below).

Mucocutaneous leishmaniasis (infections caused by *L. braziliensis*), *by intramuscular injection*, **ADULT** and **CHILD,** 20 mg/kg daily until slit-skin smears are negative and for at least 4 weeks; if inadequate response, 10–15 mg/kg every 12 hours for same period; if relapse, retreat for at least twice as long; if unresponsive to treatment, treat with pentamidine or amphotericin B (see below).

Diffuse cutaneous leishmaniasis (infections caused by *L. amazonensis*), *by intramuscular injection*, **ADULT** and **CHILD,** 20 mg/kg daily for several months after clinical improvement occurs; relapse must be expected until immunity develops.

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: one in each buttock or thigh) or by slow intravenous injection (over at least 5 minutes). It may also be administered intralesionally.

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 (rare) pancreatitis, rash; pain and thrombosis on intravenous administration; pain on intramuscular injection.

Paromomycin

Solution for intramuscular injection: 750 mg of paromomycin base present as the sulfate.

NOTE. 11 mg paromomycin base is approximately equivalent to 15 mg paromomycin sulfate.

Uses: visceral leishmaniasis unresponsive to antimonial compounds.

Contraindications: hypersensitivity to aminoglycosides; previous course of paromomycin treatment in preceding 3 months; concurrent administration of nephrotoxic or ototoxic drugs including aminoglycosides; renal impairment (Appendix 4).

Precautions: pregnancy (Appendix 2); **interactions:** Appendix 1.

Dose:

NOTE.

All doses are in terms of paromomycin base.

Visceral leishmaniasis (unresponsive to antimonial compounds), *by intramuscular injection*, **ADULT** and **CHILD** over 5 kg, 11 mg/kg daily for 21 days.

Adverse effects: injection site reactions including pain and swelling; raised aspartate aminotransferase and alanine aminotransferase; pyrexia; ototoxicity (reversible at recommended dosage), vomiting, proteinuria, raised alkaline phosphatase and blood bilirubin; nephrotoxicity and neurotoxicity including numbness, skin tingling, and muscle twitching; convulsions reported with concomitant use of aminoglycosides; neuromuscular blockage and respiratory paralysis reported following high doses of concomitant aminoglycosides.

Pentamidine

Powder for injection: 200 mg; 300 mg (isetionate) in vial.

Pentamidine is a complementary list antiprotozoal and antipneumocystis medicine.

Uses: leishmaniasis; African trypanosomiasis (section 6.5.5.1); *Pneumocystis carinii* (*Pneumocystis jiroveci*) pneumonia (section 6.5.4).

Contraindications: severe renal impairment.

Precautions: risk of severe hypotension following administration (establish baseline blood pressure and administer with patient lying down); monitor blood pressure during administration and treatment period; hypotension or hypertension; hypoglycaemia or hyperglycaemia; hepatic impairment (Appendix 5); leukopenia, thrombocytopenia, anaemia; immunodeficiency (interrupt or discontinue if acute deterioration in bone marrow, renal, or pancreatic function); renal impairment (Appendix 4); pregnancy (in potentially fatal visceral leishmaniasis, treat without delay; Appendix 2) and

breastfeeding (Appendix 3); carry out laboratory monitoring according to manufacturer's recommendations; **interactions:** Appendix 1.

Dose:

Visceral leishmaniasis (unresponsive to, or intolerant of, antimonial compounds), *by deep intramuscular injection* or *by intravenous infusion*, **ADULT** and **CHILD,** 4 mg/kg 3 times a week for 5–25 weeks or longer, until 2 consecutive splenic aspirates taken 14 days apart are negative.

Cutaneous leishmaniasis (infections caused by *L. aethiopica, L. guyanensis*), *by deep intramuscular injection* or *by intravenous infusion*, **ADULT** and **CHILD,** 3–4 mg/kg once or twice a week until the lesion is no longer visible; relapse is unusual.

Diffuse cutaneous leishmaniasis (infections caused by *L. aethiopica*), *by deep intramuscular injection* or *by intravenous infusion*, **ADULT** and **CHILD,** 3–4 mg/kg once a week, continued for at least 4 months after parasites no longer detectable in slit-skin smears; relapse frequent during first few months until immunity established.

Mucocutaneous leishmaniasis unresponsive to antimonial compounds, *by deep intramuscular injection* or *by intravenous infusion*, **ADULT** and **CHILD,** 4 mg/kg 3 times a week for 5–25 weeks or longer, until lesion is no longer visible.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions. Deep intramuscular injection is the preferred route of administration. Pentamidine is toxic; care is required in order to protect personnel during handling and administration.

Adverse effects: nephrotoxicity; acute hypotension — with dizziness, headache, breathlessness, tachycardia and syncope — following rapid intravenous injection; hypoglycaemia (may be followed by hyperglycaemia and type I diabetes mellitus); pancreatitis; also hypocalcaemia, gastrointestinal disturbances, confusion, hallucinations, arrhythmias; thrombocytopenia, leukopenia, abnormal liver function tests; anaemia; hyperkalaemia; rash including Stevens-Johnson syndrome reported; pain, local induration, sterile abscess, and muscle necrosis at injection site.

6.5.3 Antimalarial medicines

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 (see section 6.5.3.2). They include the 4-aminoquinolines (**amodiaquine** and **chloroquine**), the related arylaminoalcohols (**mefloquine** 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, two 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,
- artesunate with amodiaquine,
- artesunate with mefloquine,
- artesunate with sulfadoxine + pyrimethamine.

The most appropriate combination will depend on the levels of resistance and tolerance to individual drugs in a particular area. For example, in areas with multidrug resistant *P. falciparum*, artesunate with mefloquine or artemether + lumefantrine are the combinations of choice; in Africa, where there are concerns about the tolerability of mefloquine in children, artemether +

lumefantrine, artesunate with amodiaquine, and artesunate with sulfadoxine + pyrimethamine might be more appropriate. Patients should be advised on the importance of adhering to their prescribed regimen for the full duration of the course to ensure the most effective treatment.

Treatment failure *more than 14 days* after completion or commencement of initial treatment can be retreated with the same artemisinin-based combination (if mefloquine was included in the initial treatment, treat as a failure *within* 14 days, as below). If treatment failure occurs *within 14 days* of initial treatment, one of the following regimens may be suitable:

- a different artemisinin-based combination known to be effective in the region;
- artesunate (2 mg/kg once daily) in combination with *either* doxycycline (3.5 mg/kg once daily) *or* clindamycin (10 mg/kg twice daily) *or* tetracycline (4 mg/kg 4 times a day) [not included on the 15th WHO Model List] for 7 days;
- quinine (10 mg/kg 3 times a day) in combination with *either* doxycycline dose *or* clindamycin dose *or* tetracycline dose [not included on the 15th WHO Model List] for 7 days.

For travellers returning to non-endemic countries, one of the following regimens may be suitable (note that if malaria chemoprophylaxis was taken, a different drug should be used for treatment):

- artemether + lumefantrine (see under Artemether + lumefantrine for dose);
- quinine (10 mg/kg every 8 hours) in combination with *either* doxycycline (3.5 mg/kg once daily) *or* clindamycin (10 mg/kg twice daily), for 7 days each;
- atovaquone (15 mg/kg) with proguanil (6 mg/kg once daily for 3 days; usual adult dose, 4 tablets once daily for 3 days) [not included on the 15th WHO Model List].

Pregnancy and breastfeeding

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, then 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. Breastfeeding 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. Rectal preparations of artesunate or artemisinin [not included on the 15th WHO Model List] may be used as alternatives before transfer to a health facility for parenteral treatments. 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, section 2.1) and an antiemetic (section 17.2) 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 (except in countries in Central America and in the Island form of Hispaniola, where chloroquine and sulfadoxine + pyrimethamine still have high efficacy against *P. falciparum*). 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; 500 micrograms/kg daily for 14 days in Oceania and south-east Asia). 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.

Amodiaquine is used in combination with other antimalarials for the treatment of uncomplicated *P. falciparum* infection (see below); however, cross-resistance with chloroquine exists in some areas. Hepatitis and blood disorders were reported when amodiaquine was used for prophylaxis of malaria; patients should be told how to recognize the symptoms of these conditions and advised to seek medical help if they occur.

The combination of **sulfadoxine + pyrimethamine** is also used in combination with other antimalarials for the treatment of uncomplicated *P. falciparum* infection (see below). Resistance to sulfadoxine + pyrimethamine is now widespread, particularly in south-east Asia and South America, to a lesser extent, in east and central Africa. Because sulfonamides are associated with haemolysis and methaemoglobinaemia in neonates, quinine is preferred for chloroquine-resistant malaria during pregnancy (see below).

Mefloquine resistance is common in Cambodia, Myanmar, and Thailand, and has occurred in the Amazon region of South America and occasionally in Africa. A parenteral preparation is not available and thus it is suitable only for patients who can take drugs by mouth. It is generally well tolerated but some adverse effects have been reported (see Mefloquine below).

Quinine, given orally, is used in combination with clindamycin or doxycycline to treat relapses of *P. falciparum* infections which 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 south-east 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 are effective alternatives 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.

Amodiaquine

Tablet: 153 mg or 200 mg (as hydrochloride).

Uses: treatment of uncomplicated malaria caused by *P. falciparum* in combination with other antimalarial drugs (see also introductory note above).

Contraindications: hepatic impairment (Appendix 5); blood disorders; retinopathy.

Precautions: pregnancy (Appendix 2) and breastfeeding (Appendix 3); G6PD deficiency; avoid concurrent therapy with hepatotoxic drugs; **interactions:** Appendix 1.

PATIENT ADVICE. Patients and their carers should be told how to recognize the signs of blood disorders and advised to seek medical attention as soon as possible if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising, or bleeding develop. They should also be told how to recognize signs of hepatitis and advised to seek medical attention if symptoms such as anorexia, abnormal weight loss, asthenia, abdominal pains, fever, nausea, or vomiting develop.

Dose:

NOTE. All doses are in terms of amodiaquine base.

Treatment of uncomplicated falciparum malaria (in combination with other antimalarial drugs), *by mouth,* **ADULT** and **CHILD** over 5 months, 10 mg/kg daily for 3 days.

Adverse effects: blood disorders including leukopenia and agranulocytosis; hepatitis; gastrointestinal disturbances, visual disturbances (retinopathy associated with long-term, high-dose therapy); rarely rash, pruritus, skin pigmentation, and neuromyopathy.

Artemether

Oily injection: 80 mg/ml in 1-ml ampoule.

Uses: treatment of severe *P. falciparum* malaria in areas where quinine is ineffective (see also introductory note above).

Contraindications: first trimester of pregnancy (Appendix 2).

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 areas of quinine resistance), *by intramuscular injection*, **ADULT** and **CHILD** over 6 months, loading dose of 3.2 mg/kg, then 1.6 mg/kg daily until patient can tolerate oral medication or up to a maximum of 7 days; this is followed by a single dose of oral mefloquine 15 mg/kg (occasionally, 25 mg/kg if necessary) to effect a radical cure.

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, diarrhoea; dizziness, tinnitus, neutropenia, elevated liver enzyme values; cardiotoxicity (after high doses); neurotoxicity (in animal studies).

Artemether + lumefantrine

Tablet: 20 mg + 120 mg.

Uses: treatment of uncomplicated malaria caused by *P. falciparum* alone or with other *Plasmodium* spp. in areas with significant drug resistance (see also introductory note above).

Contraindications: breastfeeding (Appendix 3); history of arrhythmias, clinically relevant bradycardia, or congestive heart failure accompanied by reduced left ventricular ejection fraction; family history of sudden death or congenital prolongation of QT interval (see also Precautions).

Precautions: first trimester of pregnancy (Appendix 2); electrolyte disturbances; concomitant administration of drugs that prolong the QT interval; monitor patients unable to take food (greater risk of recrudescence); severe renal

impairment (Appendix 4); hepatic impairment (Appendix 5); **interactions:** Appendix 1.

SKILLED TASKS. Dizziness may impair ability to perform skilled tasks, for example, operating machinery or driving.

Dose:

Treatment of uncomplicated *falciparum* malaria:

by mouth, **ADULT** and **CHILD** over 12 years/body weight over 35 kg, initially 4 tablets followed by 5 further doses of 4 tablets each at 8, 24, 36, 48, and 60 hours (total, 24 tablets over 60 hours);

CHILD

body weight 5–14 kg, initially 1 tablet followed by 5 further doses of 1 tablet each at 8, 24, 36, 48, and 60 hours (total, 6 tablets over 60 hours);

body weight 15–24 kg, initially 2 tablets followed by 5 further doses of 2 tablets each at 8, 24, 36, 48, and 60 hours (total, 12 tablets over 60 hours);

body weight 25–34 kg, initially 3 tablets followed by 5 further doses of 3 tablets each at 8, 24, 36, 48, and 60 hours (total, 18 tablets over 60 hours).

PATIENT ADVICE. Take tablets with food; repeat dose if vomiting occurs within 1 hour of administration.

Adverse effects: abdominal pain, anorexia, diarrhoea, nausea and vomiting; headache, dizziness, sleep disorders; palpitation; arthralgia, myalgia; cough; asthenia, fatigue; pruritus, rash.

Artesunate

Injection: ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.
Tablet: 50 mg.

Uses: treatment of uncomplicated malaria caused by *P. falciparum* in combination with other antimalarials (see also introductory note above); treatment of severe malaria in areas where quinine is ineffective.

Contraindications: first trimester of pregnancy (Appendix 2).

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 drugs):

by mouth, **ADULT** and **CHILD** over 5 months, 4 mg/kg daily for 3 days;

by intravenous or *intramuscular injection*, **ADULT,** initially 2.4 mg/kg, then repeated at 12-hour intervals for 2 further doses, then once daily.

RECONSTITUTION. Artesunic acid should be dissolved in sodium bicarbonate 5% solution for injection (to form sodium artesunate), and then further diluted in 5 ml of glucose 5% solution for injection before administration; solutions should be freshly prepared prior to administration. Consult manufacturer's literature for further information.

Adverse effects: headache, nausea, vomiting, abdominal pain, diarrhoea, 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

Oral liquid: 50 mg (as phosphate or sulfate)/5 ml.
Tablet: 100 mg; 150 mg (as phosphate or sulfate).

Uses: treatment of acute malaria caused by *P. malariae, P. vivax*, and *P. ovale* (followed in *P. vivax a*nd *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 5); renal impairment (Appendix 4); pregnancy (but in acute malaria, benefit is usually considered to outweigh risk; Appendix 2) and breastfeeding (Appendix 3); may exacerbate psoriasis; neurological disorders; may aggravate myasthenia gravis; severe gastrointestinal disorders; G6PD deficiency; avoid concurrent therapy with hepatotoxic drugs; **interactions:** Appendix 1.

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, then 5 mg/kg daily on next 2 days *or* 10 mg/kg for 2 days, 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 a dose is vomited, the same amount must be readministered 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

Capsule: 100 mg (as hydrochloride).
Tablet (dispersible): 100 mg (as monohydrate).

Doxycycline is a complementary list medicine for the treatment of malaria.

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; see also introductory note above); bacterial infections (section 6.2.2); moderate acne (section 13.5).

Contraindications: pregnancy (Appendix 2); 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 4); hepatic impairment (Appendix 5); breastfeeding (Appendix 3); **interactions:** Appendix 1.

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 oesophageal 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.

Mefloquine

Tablet: 250 mg (as hydrochloride).

Uses: treatment of uncomplicated malaria due to multidrug-resistant *P. falciparum* in combination with other antimalarials (see also introductory note above); prophylaxis of malaria (see section 6.5.3.2).

Contraindications: history of neuropsychiatric disorders including depression or convulsions; hypersensitivity to quinine.

Precautions: pregnancy (use only if other antimalarials are inappropriate; Appendix 2); avoid pregnancy during, and for 3 months after, use; cardiac conduction disorders; breastfeeding (Appendix 3); not recommended for infants under 3 months (5 kg); **interactions:** Appendix 1.

NOTE. Patients should be informed about the adverse effects associated with mefloquine and, if they occur, advised to seek medical advice on alternative antimalarials.

SKILLED TASKS. Dizziness may impair ability to perform skilled tasks, for example, operating machinery or driving; effects may persist for up to 3 weeks.

Dose:

NOTE. All doses are in terms of mefloquine base.

Treatment of uncomplicated falciparum malaria (in combination with other antimalarial drugs), *by mouth*, **ADULT** and **CHILD,** 25 mg/kg usually given over 2–3 days.

Adverse effects: nausea, vomiting, diarrhoea, abdominal pain, anorexia, headache, dizziness (can be severe), loss of balance, somnolence, insomnia and abnormal dreams; neurological and psychiatric disturbances including sensory and motor neuropathies, tremor, ataxia, visual disturbances, tinnitus, and vestibular disorders; convulsions, anxiety, depression, suicidal ideation, confusion, hallucinations, panic attacks, emotional instability, aggression, agitation and psychoses; circulatory disorders, tachycardia, bradycardia, cardiac conduction disorders; muscle weakness, myalgia, arthralgia; rash, urticaria, pruritus, alopecia; disturbances in liver function tests, leukopenia, leucocytosis, thrombocytopenia; rarely Stevens-Johnson syndrome, atrioventricular block, and encephalopathy.

Primaquine

Tablet: 7.5 mg; 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 2) and breastfeeding (Appendix 3); conditions that predispose to granulocytopenia (including active rheumatoid arthritis and lupus erythematosus).

Precautions: monitor blood count (if either methaemoglobinaemia or haemolysis 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 1.

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,** 500–50 micrograms/kg as a single dose.

Adverse effects: anorexia, nausea and vomiting, abdominal pain; acute haemolytic anaemia (frequently in G6PD deficiency); rarely, methaemoglobinaemia, haemoglobinuria, agranulocytosis, granulocytopenia and leukopenia.

Quinine

Injection: 300 mg quinine hydrochloride/ml in 2-ml ampoule.
Tablet: 300 mg (quinine sulfate) or 300 mg (quinine bisulfate).

Uses: treatment of multidrug-resistant *P. falciparum* malaria, alone or in combination with other antimalarial drugs.

Contraindications: haemoglobinuria; 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 out-weigh risk, Appendix 2) and breastfeeding (Appendix 3); renal impairment (Appendix 4); G6PD deficiency; **interactions:** Appendix 1.

Dose:

NOTE. 100 mg of quinine (anhydrous base) or 169 mg quinine bisulfate or 122 mg quinine dihydrochloride or 121 mg quinine sulfate.

The 300 mg quinine bisulfate tablets provide less quinine than the 300 mg quinine sulfate or dihydrochloride tablets.

Treatment of multidrug-resistant *P. falciparum* malaria, *by mouth*, **ADULT,** 600 mg (quinine sulfate) every 8 hours for 3, 7, or 10 days; **CHILD,** 10 mg/kg (quinine sulfate) every 8 hours for 3, 7, or 10 days; duration of treatment depends on local susceptibility of *P. falciparum* and whether or not additional antimalarials are used.

PATIENT ADVICE. If all or part of a dose is vomited within one hour of administration, the same amount must be readministered 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.

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, diarrhoea, hot and flushed skin, rash, and confusion); hypersensitivity reactions including angioedema; rarely haemorrhage and asthma; hypoglycaemia (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

Tablet: 500 mg + 25 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 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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) as a single dose; **CHILD** 5–10 kg, half tablet; **CHILD** 11–20 kg, 1 tablet; **CHILD** 21–30 kg, 1½ tablets; **CHILD** 31–45 kg, 2 tablets, as a single dose.

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 anaemia, 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 is an important preventative strategy.

When possible, pregnant women should avoid travel to malarious areas; when travel is unavoidable effective prophylaxis is essential.

Chloroquine, which is usually well-tolerated at the required dosage for prophylaxis, is preferred where *P. falciparum* remains fully sensitive. The combination of proguanil with chloroquine may overcome mild chloroquine resistance (see below). 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.

Mefloquine may be used for prophylaxis in areas of high risk or where multidrug resistance has been reported. Where possible, prophylaxis should be started 2–3 weeks before travel to enable any adverse reactions to be identified before exposure (over three quarters of adverse reactions occur by the third dose) and should be continued for 4 weeks after last exposure. Mefloquine can be used for prophylaxis during the second and third trimesters; it should be used in early pregnancy only if alternative drugs are either not available or unlikely to be effective and when it is impracticable for the woman to leave the endemic area.

Doxycycline is an alternative to mefloquine in areas of high risk or where multidrug resistance has been reported; it should not be given during pregnancy.

Proguanil, a predominantly tissue schizontocide with little blood schizontocidal activity, is active against the pre-erythrocytic intrahepatic forms of the malaria-causing parasites, particularly *P. falciparum*. The latent persistent liver forms of *P. ovale* and *P. vivax* are unresponsive. However, there is evidence that proguanil may be effective against *P. vivax* only immediately after the initial infection. *P. falciparum* resistance to proguanil or related compounds can occur in malaria endemic areas and particularly where it has been used for mass prophylaxis.

Proguanil is used for prophylaxis with chloroquine in areas where there is resistance to chloroquine but a low risk of infection because it may give some protection against *P. falciparum* and may attenuate symptoms if an attack occurs. Proguanil and chloroquine can also be used prophylactically in areas of high risk or multi-drug resistance as a third choice where mefloquine or doxycycline are not appropriate.

There is no evidence that proguanil is harmful in prophylactic doses during pregnancy. Because of the vulnerability of pregnant women to falciparum malaria, it should be used at full prophylactic dosage wherever the disease is prevalent and likely to be responsive to proguanil, if chloroquine is not available. Proguanil can be given with chloroquine if chloroquine alone is unlikely to be effective. Folic acid (5 mg daily) should be given with proguanil during pregnancy.

Intermittent preventative treatment in pregnancy

Sulfadoxine + pyrimethamine is the recommended drug combination for intermittent preventative treatment in pregnancy (IPTp). All pregnant women in areas of stable, high malaria transmission should receive at least 2 doses (each at least one month apart) of sulfadoxine + pyrimethamine after quickening (the first noted movement of the fetus); *at least* 2 doses are required to achieve the optimal benefit in most women, but HIV-infected pregnant women should receive the complete 3-dose regimen.

Chloroquine

Oral liquid: 50 mg (as phosphate or sulfate)/5 ml.
Tablet: 150 mg (as phosphate or sulfate).

Uses: in non-immune individuals at risk alone or in combination with proguanil (see also introductory note above); treatment of acute malaria

caused by *P. malaria, P. vivax, P. ovale* (section 6.5.3.1); 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 5); renal impairment (Appendix 4); pregnancy (but in acute malaria, benefit is usually considered to outweigh risk; Appendix 2) and breastfeeding (Appendix 3); may exacerbate psoriasis; neurological disorders; may aggravate myasthenia gravis; severe gastrointestinal disorders; G6PD deficiency; avoid concurrent therapy with hepatotoxic drugs; **interactions:** Appendix 1.

Dose:

NOTE. All doses are in terms of the chloroquine base.

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 readministered immediately.

Treatment of acute malaria (in patients unable to take chloroquine by mouth), *by very slow intravenous infusion* (over at least 8 hours), **ADULT** and **CHILD,** 10 mg/kg as an initial dose, then 2 further infusions of 5 mg/kg at 8-hour intervals (as soon as patient is able to take chloroquine by mouth, discontinue infusions and complete the course with oral preparations total dose, 25 mg/kg over 3 days); *by intramuscular* or *by subcutaneous injection* (only when intravenous infusion facilities not available) **ADULT** and **CHILD,** 2.5 mg/kg every 4 hours or 3.5 mg/kg every 6 hours (until total dose of 25 mg/kg administered).

Prophylaxis of malaria, *by mouth*, **ADULT,** 300 mg once a week; **CHILD,** 5 mg/kg once a week.

PATIENT ADVICE. Inform travellers 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: 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

Capsule or tablet: 100 mg (hydrochloride).

Uses: short-term prophylaxis of multidrug-resistant *P. falciparum* malaria (see also introductory notes above); adjunct in the treatment 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 2); 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 4); hepatic impairment (Appendix 5); breastfeeding (Appendix 3); **interactions:** Appendix 1.

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.

PATIENT ADVICE. Capsules should be swallowed whole with plenty of fluid while sitting or standing to prevent oesophageal irritation. May be given with food or milk to counter gastric irritation.

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.

Mefloquine

Tablet: 250 mg (as hydrochloride).

Uses: short-term prophylaxis of multiple-resistant *P. falciparum* malaria (see also introductory note above); treatment of uncomplicated malaria due to multiple-resistant *P. falciparum* (section 6.5.3.1).

Contraindications: history of neuropsychiatric disorders including depression or convulsions; hypersensitivity to quinine.

Precautions: early pregnancy (use only if other antimalarials are inappropriate; Appendix 2), avoid pregnancy during and for 3 months after use; cardiac conduction disorders; avoid for prophylaxis in severe hepatic impairment (Appendix 5) and in epilepsy; breastfeeding (Appendix 3); not recommended for infants under 3 months (5 kg); **interactions:** Appendix 1.

NOTE. Patients should be informed about the adverse effects associated with mefloquine and, if they occur, advised to seek medical advice on alternative antimalarials.

SKILLED TASKS. Dizziness may impair ability to perform skilled tasks, for example, operating machinery or driving; effects may persist for up to 3 weeks.

Dose:

NOTE. All doses are in terms of mefloquine base.

Prophylaxis of malaria, *by mouth*, **ADULT,** 250 mg once a week; **CHILD** over 5 kg, 5 mg/kg once a week; prophylaxis should start 1–3 weeks before travel to a malaria-endemic area and continue for 4 weeks after the last exposure (see also introductory note above).

PATIENT ADVICE. Inform travellers 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.

Adverse effects: nausea, vomiting, diarrhoea, abdominal pain, anorexia, headache, dizziness (can be severe), loss of balance, somnolence, insomnia and abnormal dreams; neurological and psychiatric disturbances including sensory and motor neuropathies, tremor, ataxia, visual disturbances, tinnitus, and vestibular disorders; convulsions, anxiety, depression, suicidal ideation, confusion, hallucinations, panic attacks, emotional instability, aggression, agitation and psychoses; circulatory disorders, tachycardia, bradycardia, cardiac conduction disorders; muscle weakness, myalgia, arthralgia; rash, urticaria, pruritus, alopecia; disturbances in liver function tests, leukopenia, leucocytosis, thrombocytopenia; rarely, Stevens-Johnson syndrome, atrioventricular block, and encephalopathy.

Proguanil

Tablet: 100 mg (hydrochloride).

Uses: prophylaxis of malaria, in combination with chloroquine.

Contraindications: use in areas of known resistance to either proguanil or pyrimethamine.

Precautions: renal impairment (Appendix 4); pregnancy (folate supplements required, Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Prophylaxis of malaria, *by mouth*, **ADULT,** 200 mg daily, after food; **CHILD** under 1 year, 25 mg daily; **CHILD** 1–4 years, 50 mg daily; **CHILD** 5–8 years, 100 mg daily; **CHILD** 9–14 years, 150 mg daily.

PATIENT ADVICE. Inform travellers 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 area.

Adverse effects: mild gastric intolerance, diarrhoea, constipation; occasional mouth ulcers and stomatitis; rarely skin reactions and hair loss, cholestasis, vasculitis, and hypersensitivity reactions such as urticaria and angioedema.

6.5.4 Anti-pneumocystosis and antitoxoplasmosis medicines

Pneumocystosis

Pneumocystis carinii (*Pneumocystis jiroveci*) is classified as a protozoan although there is some evidence to suggest that it is a fungus. *Pneumocystis 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** 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 [not included on the 15th WHO Model List] 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 anaemia associated with these drugs (see section 10.1).

Pentamidine

Tablet: 200 mg; 300 mg.

Pentamidine is a complementary list antipneumocystosis medicine.

Uses: *Pneumocystis carinii* (*Pneumocystis jiroveci*) pneumonia unresponsive to sulfamethoxazole + trimethoprim; leishmaniasis (section 6.5.2); African trypanosomiasis (section 6.5.5.1).

Contraindications: severe renal impairment

Precautions: risk of severe hypotension following administration (establish baseline blood pressure and administer with patient lying down); monitor blood pressure during administration and treatment period; hypotension or hypertension; hypoglycaemia or hyperglycaemia; hepatic impairment (Appendix 5); renal impairment (Appendix 4); leukopenia, thrombocytopenia, anaemia; immunodeficiency (interrupt or discontinue if acute deterioration in bone marrow, renal, or pancreatic function); in potentially fatal *P. carinii* (*P. jiroveci*) pneumonia, treat without delay; pregnancy (Appendix 2)] and breastfeeding (Appendix 3); carry out laboratory monitoring according to manufacturer's recommendations; **interactions:** Appendix 1.

Dose:

Treatment of *P. carinii* (*P. jiroveci*) pneumonia, *by slow intravenous infusion* or *by deep intramuscular injection*, **ADULT** and **CHILD,** 4 mg/kg daily for at least 14 days.

Prophylaxis of *P. carinii* (*P. jiroveci*) pneumonia, *by slow intravenous infusion*, **ADULT** and **CHILD,** 4 mg/kg once every 4 weeks; *by inhalation of nebulized solution*, **ADULT,** 300 mg as a single dose once every 4 weeks; **CHILD,** 4 mg/kg as a single dose once every 4 weeks.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions. Pentamidine is toxic; care is required in order to protect personnel during handling and administration.

Adverse effects: nephrotoxicity; acute hypotension — with dizziness, headache, breathlessness, tachycardia and syncope — following rapid intravenous injection; hypoglycaemia (may be followed by hyperglycaemia and type I diabetes mellitus); pancreatitis; also hypocalcaemia, gastrointestinal disturbances, confusion, hallucinations, arrhythmias; thrombocytopenia, leukopenia, abnormal liver function tests; anaemia; hyperkalaemia; rash including Stevens-Johnson syndrome reported; pain, local induration, sterile abscess, and muscle necrosis at injection site.

Pyrimethamine

Tablet: 25 mg.

Uses: toxoplasmosis (with sulfadiazine); malaria (with sulfadoxine; see section 6.5.3.1).

Contraindications: hepatic (Appendix 5) and renal impairment (Appendix 4).

Precautions: pregnancy (avoid in first trimester but can be given in later pregnancy if danger of congenital transmission; Appendix 2) and breastfeeding (Appendix 3); blood counts required with prolonged treatment; give folate supplements throughout treatment; **interactions:** Appendix 1.

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 haematopoiesis with high doses; megaloblastic anaemia; rash; insomnia; gastrointestinal disturbances.

Sulfamethoxazole + trimethoprim

Injection: 80 mg + 16 mg/ml in 5-ml and 10-ml ampoules.

Uses: *Pneumocystis carinii* (*Pneumocystis jiroveci*) pneumonia; bacterial infections (section 6.2.2).

Contraindications: hypersensitivity to sulfonamides or trimethoprim; porphyria.

Precautions: renal impairment (avoid if severe; Appendix 4); hepatic impairment (avoid if severe; Appendix 5); 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; the elderly; asthma; G6PD deficiency; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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: nausea, vomiting, diarrhoea, headache; hypersensitivity reactions including rash, pruritus, photosensitivity reactions, exfoliative dermatitis, and erythema nodosum; rarely erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis; systemic lupus erythematosus, myocarditis, serum sickness; crystalluria — resulting in haematuria, oliguria, and anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, purpura (discontinue immediately); liver damage, pancreatitis, antibiotic-associated colitis, eosinophilia, cough and shortness of breath, pulmonary infiltrates, aseptic meningitis, depression, convulsions, ataxia, tinnitus, vertigo, dizziness, hallucinations, and electrolyte disturbances also reported; megaloblastic anaemia due to trimethoprim.

6.5.5 Antitrypanosomal medicines

6.5.5.1 African trypanosomiasis

African trypanosomiasis, or sleeping sickness, is a protozoan infection which is transmitted by *Glossina* spp. (tsetse flies). Two subspecies of *Trypanosoma brucei* — *T. brucei gambiense* and *T. brucei rhodesiense* — produce distinctive clinical forms of the disease. The early stage of African trypanosomiasis results from infection of the blood stream and lymph nodes. The late meningoencephalitic stage results from infection of the central nervous system. Signs of the later stage develop within a few weeks in *T. brucei rhodesiense* infection but only after several months or years in *T. brucei gambiense* infection.

Treatment of early-stage infections of *T. brucei rhodesiense* with **suramin sodium** and *T. brucei gambiense* with **pentamidine** can be curative if started before the

central nervous system has become involved. In areas where pentamidine resistance occurs, suramin sodium may be used for *T. brucei gambiense* infection.

Eflornithine is used for the treatment of *T. brucei gambiense* infection that has progressed to meningoencephalitic involvement. Eflornithine is considerably less neurotoxic than the alternative, melarsoprol, but requires a more intensive administration schedule. If relapse occurs after treatment with eflornithine, a course of melarsoprol treatment should be considered.

Melarsoprol is used in *T. brucei rhodesiense* patients with meningoencephalitic involvement or in *T. brucei gambiense* patients with meningoencephalitic involvement when eflornithine treatment has failed or is unavailable. Several treatment regimens for adults and children are currently used in the absence of clear evidence that one is better than another. Most treatment regimens have low starting doses, which might be preferred for children and debilitated patients; these regimens increase to a maximum of 3.6 mg/kg daily and are given in short courses of 3–4 days with an interval of 7–10 days. The effectiveness of 2.2 mg/kg daily for 10 days has been demonstrated for *T. brucei gambiense* and might be preferred for its conciseness, particularly in epidemic situations with limited resources.

In recent years, an increasing number of melarsoprol treatment failures due to drug resistance have been reported in several countries.

Following treatment of African trypanosomiasis, patients should be followed up at 6-month intervals over a period of 24 months. Monitoring of leukocytes, total protein content and trypanosome presence in CSF is recommended in order to evaluate treatment efficacy.

Eflornithine

Injection: 200 mg (hydrochloride)/ml in 100-ml bottle.

Uses: treatment of meningoencephalitic stages of *T. brucei gambiense* infection.

Contraindications: pregnancy; breastfeeding.

Precautions: hospitalization and close supervision required throughout treatment; monitor complete blood and platelet counts for signs of bone marrow suppression (severe anaemia, leukopenia, or thrombocytopenia requires an interruption in treatment until there is evidence of bone marrow recovery); renal impairment (Appendix 4).

Dose:

Treatment of meningoencephalitic *T. brucei gambiense* infections, *by intravenous infusion*, **ADULT,** 100 mg/kg over 45 minutes every 6 hours for 14 days; **CHILDREN** less than 12 years old or under 35 kg, 150 mg/kg over 45 minutes every 6 hours for 14 days.

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: diarrhoea, anaemia, leukopenia, thrombocytopenia, convulsions; impaired hearing reported; less commonly vomiting, anorexia, alopecia, abdominal pain, headache, facial oedema, eosinophilia, and dizziness (reversible on treatment withdrawal).

Melarsoprol

Injection: 3.6% solution, 5-ml ampoule (180 mg of active compound).

Uses: treatment of meningoencephalitic stage of *T. brucei rhodesiense* and *T. brucei gambiense* infections.

Contraindications: pregnancy (Appendix 2); during influenza epidemics (increased risk of reactive encephalopathy in febrile patients).

Precautions: hospitalization and close medical supervision required throughout treatment; episodes of reactive encephalopathy (suspend treatment); treat intercurrent infections such as pneumonia and malaria before melarsoprol administration; malnutrition (if possible, correct with a protein-rich diet); G6PD deficiency; leprosy (may precipitate erythema nodosum).

Dose:

Treatment of *T. brucei rhodesiense* and *T. brucei gambiense* with meningo-encephalitic involvement (see note above), *by slow intravenous injection*, **ADULT** and **CHILD,** dose gradually increased from 1.2 mg/kg to maximum of 3.6 mg/kg daily in courses of 3–4 days with intervals of 7–10 days between courses; alternatively for *T. brucei gambiense* infection, 2.2 mg/kg daily for 10 days.

ADMINISTRATION. Injection is very irritant (avoid extravasation). Patients should remain supine and fast for at least 5 hours after injection.

Adverse effects: fatal reactive encephalopathy characterized by headache, tremor, slurred speech, convulsions, and ultimately coma (occurs in 3–8% of patients, usually at the end of the first 3–4 days of treatment); myocardial damage; albuminuria; hypertension; hypersensitivity reactions; agranulocytosis; dose-related renal and hepatic impairment; hyperthermia, urticaria, headache, diarrhoea, and vomiting (more common in late stage of treatment).

Pentamidine

Powder for injection: 200 mg (pentamidine isetionate) in vial.

Uses: treatment of haemolymphatic stage of *T. brucei gambiense* infection; adjunct to melarsoprol in meningoencephalitic stage of *T. brucei gambiense* infection; leishmaniasis (section 6.5.2); *Pneumocystis carinii* (*Pneumocystis jiroveci*) pneumonia (section 6.5.4).

Contraindications: severe renal impairment; *T. brucei rhodesiense* infection (since primary resistance has been observed).

Precautions: examine cerebrospinal fluid before treatment (pentamidine is not likely to be effective if leukocyte count is greater than 5 cells/mm^3, total protein is greater than 37 mg/100 ml, or trypanosomes are detected in centrifuge deposits); risk of severe hypotension following administration (establish baseline blood pressure and administer with patient lying down); monitor blood pressure during administration and treatment period; hypotension or hypertension; hepatic impairment (Appendix 5); hypoglycaemia or hyperglycaemia; leukopenia; thrombocytopenia; anaemia; immunodeficiency (interrupt or discontinue if acute deterioration in bone marrow, or in renal or pancreatic function); renal impairment (Appendix 4); pregnancy (however, treatment should not be withheld, even if there is evidence of meningoencephalitic involvement, as melarsoprol is contraindicated; Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Treatment of haemolymphatic stage of *T. brucei gambiense* infection, *by intramuscular injection*, **ADULT** and **CHILD,** 4 mg/kg daily or on alternate days for a total of 7–10 doses.

Treatment of meningoencephalitic stage of *T. brucei gambiense* (prior to melarsoprol), *by intramuscular injection*, **ADULT** and **CHILD,** 4 mg/kg daily on days one and two.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions. Pentamidine is toxic; care is required in order to protect personnel during handling and administration.

Adverse effects: nephrotoxicity; acute hypotension; hypoglycaemia (may be followed by hyperglycaemia and type I diabetes mellitus); pancreatitis; also hypocalcaemia, gastrointestinal disturbances, confusion, hallucinations, arrhythmias; thrombocytopenia, leukopenia, abnormal liver function tests; anaemia; hyperkalaemia; rash including Stevens-Johnson syndrome reported; pain, local induration, sterile abscess, and muscle necrosis at injection site.

Suramin sodium

Powder for injection: 1 g in vial.

Uses: treatment of haemolymphatic stage of *T. brucei rhodesiense* infections; onchocerciasis (section 6.1.2).

Contraindications: previous anaphylaxis or suramin sensitivity; severe liver (Appendix 5) or renal function impairment (Appendix 4); the elderly or debilitated.

Precautions: administer only under close medical supervision in hospital and with general condition of patient improved as far as possible before treatment; first dose (possible loss of consciousness; see under Dose, below); maintain satisfactory food and fluid intake during treatment; urine tests before and weekly during treatment (reduce dose if moderate albuminuria, discontinue immediately if severe albuminuria or casts in urine); pregnancy (however, treatment should not be withheld, even if there is evidence of meningoencephalitic involvement, as melarsoprol is contraindicated; Appendix 2).

Dose:

Treatment of haemolymphatic *T. brucei rhodesiense* and *T. brucei gambiense* infections, *by slow intravenous injection*, **ADULT** and **CHILD,** 5 mg/kg on day 1, 10 mg/kg on day 3, and 20 mg/kg on days 5, 11, 17, 23, and 30.

RECONSTITUTION OF INJECTION. Reconstitute in water for injections to produce a final concentration of 10%.

FIRST (TEST) DOSE. Administer first dose with particular caution; wait at least 1 minute after injecting the first few microlitres; inject the next 0.5 ml over 30 seconds and wait 1 minute; inject the remainder over several minutes.

Adverse effects: rarely immediate and potentially fatal reaction with nausea, vomiting, shock, and loss of consciousness during first dose (see note above); albuminuria; abdominal pain; severe diarrhoea; stomal ulceration; exfoliative dermatitis; fever; tiredness; anorexia; malaise; polyuria; thirst; raised liver enzyme values; paraesthesia and hyperaesthesia of palms and soles.

6.5.5.2 American trypanosomiasis

American trypanosomiasis (Chagas disease) is caused by the protozoan parasite *Trypanosoma cruzi*, which is carried by reduviid or triatomine bugs that feed on human blood. The acute febrile phase of the disease frequently passes unrecognized. Occasionally, however, infection follows a fulminating course, terminating in a fatal myocarditis and meningoencephalitis. In about half of the

surviving cases, and after a latent interval ranging from 10 to more than 20 years, chronic myopathy degeneration results in arrhythmias, cardiac enlargement and, less frequently, oesophageal and colonic dilatation. At this stage, only symptomatic treatment is of benefit.

At present, the only therapeutic agents of value are **benznidazole** and **nifurtimox**. Both suppress parasitaemia and are efficacious during the early stages of infection.

Safe use of both of these drugs in pregnancy has not been established and treatment should be deferred until after the first trimester. At this juncture, treatment should be instituted immediately to avoid the risk of congenital transmission.

Studies are in progress to determine whether benznidazole and nifurtimox have any influence on the later manifestations of the disease. Symptomatic treatment may be necessary in advanced cases.

Benznidazole

Tablet: 100 mg.

Uses: acute American trypanosomiasis (Chagas disease).

Contraindications: early pregnancy (Appendix 2).

Precautions: hepatic, renal, or haematological insufficiency (require close medical supervision); monitor blood count, especially leukocytes, throughout treatment.

Dose:

Acute American trypanosomiasis (Chagas disease), *by mouth*, **ADULT,** 5–7 mg/kg daily in 2 divided doses for 60 days; **CHILD** up to 12 years, 10 mg/kg daily in 2 divided doses for 60 days.

Adverse effects: rash (if severe and accompanied by fever and purpura, discontinue treatment); nausea, vomiting, abdominal pain; dose-related paraesthesia and peripheral neuritis (discontinue treatment); leukopenia; rarely agranulocytosis.

Nifurtimox

Tablet: 30 mg; 120 mg; 250 mg.

Uses: acute American trypanosomiasis (Chagas disease).

Contraindications: early pregnancy (Appendix 2).

Precautions: history of convulsions or psychiatric disease (requires close medical supervision); avoid alcohol to reduce incidence and severity of

adverse effects; co-administer aluminium hydroxide to reduce gastrointestinal irritation.

Dose:

Acute American trypanosomiasis (Chagas disease), *by mouth*, **ADULT,** 8–10 mg/kg daily in 3 divided doses for 90 days; **CHILD,** 15–20 mg/kg daily in 4 divided doses for 90 days.

Adverse effects: anorexia, loss of weight, nausea, vomiting, gastric pain, insomnia, headache, vertigo, excitability, myalgia, arthralgia; dose-related convulsions (reduce dose); peripheral neuritis (may require discontinuation); rash and other allergic reactions.

SECTION 7:
Antimigraine medicines

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Chronic recurrent headache is associated with many disorders, both somatic and psychogenic. An accurate diagnosis must consequently be made before appropriate treatment can be initiated for migraine. Untreated, migraine attacks last for several hours and sometimes for 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).

7.1 For treatment of acute attack

Treatment of acute attacks may be non-specific using simple analgesics; if nausea and vomiting are features of the attack, an antiemetic 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 include analgesics, $5HT_1$ agonists [not included on the 15th WHO Model List] and ergotamine [not included on the 15th WHO Model List]) is associated with medication-overuse headache (analgesic-induced headache); therefore, increasing consumption of these medicines needs 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 (NSAIMs), such as ibuprofen (see section 2.1) (see also attached notes). 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 antiemetic, 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 (see also section 17.2).

Specific antimigraine drugs, such as the $5HT_1$ agonist, sumatriptan [not included on the 15th WHO Model List], 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 which contain barbiturates or codeine are also undesirable since they may cause physical dependence and withdrawal headaches.

Acetylsalicylic acid

Tablet: 300–500 mg.

Also known as Aspirin.

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 NSAIM; children and adolescents under 16 years (risk of Reye syndrome, see section 2.1); previous or active peptic ulceration; haemophilia and other bleeding disorders; not for treatment of gout.

Precautions: asthma, allergic disease; renal impairment (Appendix 4); hepatic impairment (Appendix 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3); the elderly; G6PD-deficiency; dehydration; **interactions**: Appendix 1.

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.

Treatment of acute migraine attack, *by rectum*, **ADULT,** 600–900 mg inserted at first sign of attack, repeated every 4 hours if necessary; maximum, 3.6 g daily; **CHILD** under 16 years, not recommended.

Adverse effects: generally mild and infrequent but high incidence of gastrointestinal irritation with slight asymptomatic blood loss; increased bleeding time; bronchospasm and skin reactions in hypersensitive patients; for adverse effects associated with higher doses, see also section 2.1.

Paracetamol

Tablet: 300–500 mg.

Also known as Acetaminophen.

Uses: acute migraine attacks, tension headache; mild to moderate pain, pyrexia (section 2.1).

Precautions: hepatic impairment (Appendix 5); renal impairment (Appendix 4); alcohol dependence; pregnancy (Appendix 2) and breastfeeding (Appendix 3); overdosage: section 4.2; **interactions:** Appendix 1.

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 (see section 12.1), are generally preferred. Tricyclic antidepressants, such as amitriptyline (section 24.2.1) or calcium-channel blocking drugs such as verapamil (section 12.1) may be of value.

Propranolol

Tablet: 20 mg; 40 mg (hydrochloride).

Propranolol is a representative beta-adrenoceptor antagonist. Various medicines can serve as alternatives.

Uses: prophylaxis of migraine.

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; phaeochromocytoma.

Precautions: first-degree atrioventricular block; renal impairment (Appendix 4); liver disease (Appendix 5); pregnancy (Appendix 2), and breastfeeding (Appendix 3); portal hypertension; diabetes mellitus; myasthenia gravis; history of hypersensitivity [increased reaction to allergens and reduced response to epinephrine (adrenaline)]; **interactions:** Appendix 1.

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, 80–160 mg daily; **CHILD** under 12 years, 20 mg 2–3 times daily.

Adverse effects: bradycardia, heart failure, hypotension, conduction disorders, bronchospasm, peripheral vasoconstriction, exacerbation of intermittent claudication and Raynaud phenomenon; gastrointestinal disturbances, fatigue, sleep disturbances including nightmares; rarely rash, dry eyes (reversible), sexual dysfunction, and exacerbation of psoriasis.

SECTION 8:
Antineoplastic, immunosuppressives and medicines used in palliative care

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8.1 Immunosuppressive medicines

NOTE. WHO advises that this class of drugs is for use only when adequate resources and specialist care are available. Specific expertise, diagnostic precision, individualization of dosage, and special equipment are required for their proper use.

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 which 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 (section 8.3) have significant immunosuppressant activity and can also be used to prevent rejection of organ transplants.

Azathioprine

Powder for injection: 100 mg (as sodium salt) in vial.
Tablet: 50 mg.

Azathioprine is a complementary list immunosuppressive medicine.

Uses: to prevent rejection in transplant recipients; rheumatoid arthritis (section 2.4); inflammatory bowel disease (section 17.3).

Contraindications: hypersensitivity to azathioprine and mercaptopurine; breastfeeding (Appendix 3).

Precautions: monitor for toxicity throughout treatment; full blood counts necessary every week (or more frequently with higher doses and in renal or hepatic impairment) for the first 4 weeks of treatment, and at least every 3 months thereafter; reduce dose in the elderly; pregnancy (Appendix 2); renal impairment (Appendix 4); liver disease (Appendix 5); **interactions:** Appendix 1.

BONE MARROW SUPPRESSION. Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example, unexplained bruising or bleeding, or infection.

Dose:

Transplant rejection, *by mouth* or *by intravenous injection* (over at least 1 minute and followed by 50 ml sodium chloride intravenous infusion) or *by intravenous infusion*, **ADULT,** up to 5 mg/kg on day of surgery, then reduced according to response to 1–4 mg/kg daily for maintenance.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

NOTE. Intravenous injection is alkaline and very irritant; the intravenous route should therefore only be used if oral administration is not possible.

Adverse effects: hypersensitivity reactions including malaise, dizziness, vomiting, fever, muscular pains, arthralgia, rash, hypotension, or interstitial nephritis call for immediate withdrawal; haematological toxicity including leukopenia and thrombocytopenia (reversible upon withdrawal); liver impairment, cholestatic jaundice; hair loss; increased susceptibility to infections and colitis in patients also receiving corticosteroids; nausea; rarely pancreatitis, pneumonitis, and hepatic veno-occlusive disease.

Ciclosporin

Capsule: 25 mg.
Concentrate for injection: 50 mg/ml in 1-ml ampoule for organ transplantation.

Ciclosporin is a complementary list immunosuppressive medicine.

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 5); monitor blood pressure (discontinue if hypertension cannot be controlled by antihypertensives); monitor serum potassium, particularly if marked renal impairment (risk of hyperkalaemia); monitor serum

magnesium; hyperuricaemia; measure blood lipids before and during treatment; avoid in porphyria; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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.

Concentrate for infusion may contain polyethoxylated castor oil, which has been associated with anaphylaxis; observe patient for 30 minutes after starting infusion and then at frequent intervals.

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); slowly reduced to lowest effective dose according to proteinuria and serum creatinine measurements for maintenance; discontinue after 3 months if no improvement (after 6 months in membranous glomerulonephritis).

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

CONVERSION. Any conversion between brands should be undertaken very carefully, and the manufacturer consulted for further information.

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 hyperkalaemia, and hypomagnesaemia; hepatic dysfunction; hyperuricaemia; hypercholesterolaemia; hyperglycaemia, hypertension (especially in heart

transplant patients); increased incidence of malignancies and lymphoproliferative disorders; increased susceptibility to infections due to immunosuppression; gastrointestinal disturbances; gingival hyperplasia; hirsutism; fatigue; allergic reactions; thrombocytopenia (sometimes with haemolytic uraemic syndrome); also mild anaemia, tremors, convulsions, neuropathy; dysmenorrhoea or amenorrhoea; pancreatitis, myopathy or muscle weakness; cramp; gout; oedema; headache.

8.2 Cytotoxic medicines

NOTE. WHO advises that adequate resources and specialist supervision are a prerequisite for the introduction of this class of drugs. Specific expertise, diagnostic precision, individualization of dosage and special equipment are required for their proper use.

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 tumours, 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.

The following information provides basic background information on drugs that have specific anti-tumour activity. These are toxic drugs which should be used with great care and close monitoring. The specific doses and details of contraindications, precautions, and adverse effects for the individual cytotoxic drugs have been omitted since 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 breastfeeding. 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. Local policies for the handling and reconstitution of cytotoxic drugs should be strictly adhered to; also all waste, including patient's body fluids and excreta (and any material contaminated by them) should be treated as hazardous.

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 (section 13.3). The manufacturer's literature should also be consulted for more specific information.

Adverse effects

Cytotoxic drugs have a 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. Nausea and vomiting following administration of cytotoxic drugs and abdominal radiotherapy are often distressing and may compromise further treatment. Symptoms may be acute (occurring within 24 hours of treatment), delayed (first occurring more than 24 hours after treatment), or anticipatory (occurring before subsequent doses). Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management.

Susceptibility to drug-induced nausea and vomiting varies among patients; those more affected include women, patients under 50 years, anxious patients, and those who suffer from motion sickness. Repeated exposure to the cytotoxic therapy also increases susceptibility.

Cytotoxic drugs associated with a low risk of emesis include etoposide, fluorouracil, low-dose methotrexate, and the vinca alkaloids; those with an intermediate risk include lower doses of cyclophosphamide, doxorubicin, and high-dose methotrexate; cisplatin, high-dose cyclophosphamide, and dacarbazine tend to have the highest risk of emesis.

For patients at a low risk of emesis, pretreatment with an oral phenothiazine (for example, chlorpromazine, section 24.1), continued for up to 24 hours after chemotherapy, is often helpful. For patients at a higher risk, dexamethasone, 6–10 mg by mouth (section 18.1) may be added before chemotherapy. For patients at a high risk of emesis or when other therapies are ineffective, high doses of intravenous metoclopramide (section 17.2) may be used.

Dexamethasone is the drug of choice for the prevention of delayed symptoms; it is used alone or in combination with metoclopramide (see also section 17.2).

Good symptom control is the best way to prevent anticipatory symptoms and the addition of diazepam (sections 1.3 and 24.3) to antiemetic therapy is helpful because of its sedative, anxiolytic, and amnesic effects.

Hyperuricaemia. Hyperuricaemia may complicate treatment of conditions such as non-Hodgkin lymphomas and leukaemia. Renal damage may result from the formation of uric acid crystals. Patients should be adequately hydrated and hyperuricaemia may be managed with allopurinol (section 2.3), initiated 24 hours before cytotoxic treatment and continued for 7–10 days afterwards.

Alopecia. Alopecia is common during treatment with cytotoxic drugs. There is no drug treatment, but the condition often reverses spontaneously once treatment has stopped.

Oral mucositis. Oral mucositis is common during cancer chemotherapy, particularly with fluorouracil, methotrexate, and the anthracyclines. Prevention of a sore mouth is important, because once it has developed treatment is much less effective. Brushing teeth with a soft brush 2–3 times daily and rinsing the mouth frequently are probably the most effective preventative measures. Sucking ice-chips during short infusions of fluorouracil is also helpful. Treatment involves regular use of saline mouthwashes. Generally mucositis is self-limiting, but it can be a focus for blood-borne infection in the absence of good oral hygiene. Any pain caused by mucositis should be dealt with effectively.

Alkylating medicines

Alkylating medicines are among the most widely used drugs in cancer chemotherapy. They act by damaging DNA and therefore interfering with cell replication. However, there are 2 complications. Firstly, they affect gametogenesis and may cause permanent male sterility; in women, the reproductive span may be shortened by the onset of a premature menopause.

Secondly, they are associated with a marked increase in the incidence of acute non-lymphocytic leukaemia, in particular when combined with extensive radiation therapy.

Cyclophosphamide requires hepatic activation; it can therefore be given orally and is not vesicant when given intravenously. Like all alkylating drugs its major toxic effects are myelosuppression, alopecia, nausea and vomiting. It can also cause haemorrhagic cystitis; an increased fluid intake for 24–48 hours will help to avoid this complication. Cyclophosphamide is used either as part of treatment or as an adjuvant in non-Hodgkin lymphomas, breast cancer, childhood leukaemia, and ovarian cancer. It is also used in several palliative regimens.

Chlorambucil is used to treat chronic lymphocytic leukaemia, non-Hodgkin lymphoma, Hodgkin disease, and Waldenstrom (primary) macroglobulinaemia. Adverse effects, apart from bone marrow suppression, are uncommon. However, severe widespread rash can develop and may progress to Stevens-Johnson syndrome or toxic epidermal necrolysis. If a rash occurs, further treatment with chlorambucil is contraindicated.

Cytotoxic antibiotics

Bleomycin is used in regimens for the treatment of Hodgkin disease and testicular cancer. It has several antineoplastic drug toxicities; it is known to cause dose-related pneumonitis and fibrosis which can be fatal, and is associated with rare acute hypersensitivity reactions. Cutaneous toxicity has also been reported.

Doxorubicin is a widely used anthracycline antibiotic used to treat acute leukaemias, lymphomas, and a variety of solid tumours. Doxorubicin also plays a palliative role in the treatment of other malignancies. The primary toxic effects are myelosuppression, alopecia, nausea, and vomiting, and dose-related cardiomyopathy. It is also vesicant and can cause severe skin ulceration on extravasation. Liposomal formulations of doxorubicin [not included on the 15th WHO Model List] are now available. They may reduce the incidence of cardiotoxicity and local necrosis, but severe infusion reactions and hand–foot syndrome may occur.

Dactinomycin is used to treat paediatric cancers. Its toxicity is similar to that of doxorubicin, but it is not cardiotoxic.

Daunorubicin is used in acute leukaemias. Its toxicity is similar to that of doxorubicin.

Antimetabolites and related therapy

Cytarabine is used in the treatment of acute leukaemia; children may tolerate high doses better than adults. Its effects are highly dependent upon the

schedule of administration. It causes myelosuppression, mucositis, and in high doses, central neurotoxicity.

Fluorouracil is primarily used in the adjuvant treatment of colorectal and breast cancer. It is also employed in the palliative treatment of other malignancies. It causes myelosuppression and palmar–plantar syndrome (erythema and painful desquamation of the hands and feet). When its action is modified by other drugs (such as calcium folinate), its toxicity profile can change; mucositis and diarrhoea may be significant problems. Central neurotoxicity can also occur.

Mercaptopurine is frequently used in the therapy of childhood leukaemia. It is administered orally and toxic effects include myelosuppression, nausea, hepatotoxicity and rarely pancreatitis.

Methotrexate is used to treat a variety of malignancies and it plays a major role as an adjuvant for the treatment of breast cancer. Like fluorouracil, methotrexate is myelotoxic, but nausea and vomiting are minimal. It also causes mucositis. Renal impairment reduces methotrexate excretion and can exacerbate toxicity.

Calcium folinate is used to counteract the folate-antagonist action of methotrexate and thus speed recovery from methotrexate-induced mucositis or myelosuppression. Calcium folinate also enhances the therapeutic effects of fluorouracil when the 2 are used together in metastatic colorectal cancer.

Vinca alkaloids and etoposide

The vinca alkaloids, **vinblastine** and **vincristine**, are primarily used in the treatment of acute leukaemias. Vinblastine is also used for Hodgkin disease and some solid tumours. Vincristine is also used in the management of non-Hodgkin lymphomas. Both can cause neurotoxicity, but this is more of a problem with vincristine. Myelosuppression is more common with vinblastine. Vinblastine and vincristine are for *intravenous injection only*. Inadvertent intrathecal administration causes severe neurotoxicity which is usually fatal.

Etoposide is an important component of the treatment of testicular carcinoma, and is also used in several regimens for lung cancers and lymphomas. It causes myelosuppression and alopecia and it can cause hypotension during infusion. It does not produce significant nausea and vomiting.

Other antineoplastic medicines

The enzyme, **asparaginase,** is an important component in the management of childhood leukaemia, but is not used in any other malignancy. Its toxicity profile is broad and the drug must be carefully administered because of the risk of anaphylaxis.

Cisplatin is a platinum compound which is used alone or in combination with other cytotoxic drugs for the treatment of testicular, lung, cervical, bladder,

head and neck, and ovarian cancer. Cisplatin is myelosuppressive and also produces slight alopecia; it also causes severe dose-related nausea and vomiting, and is nephrotoxic and neurotoxic. Nephrotoxicity can be reduced by maintaining high urine output during cisplatin administration and immediately afterwards, but neurotoxicity is often dose-limiting.

Dacarbazine, thought to act as an alkylating drug, is a component of a regimen for Hodgkin disease. It is also used in the palliative therapy of metastatic malignant melanoma. Its major toxic effects are myelosuppression, and severe nausea and vomiting.

Procarbazine is used in the treatment of advanced Hodgkin disease. Toxic effects include myelosuppression, nausea, and vomiting, central nervous system symptoms, and depression. Procarbazine possesses a weak monoamine oxidase inhibitory effect but dietary restriction is not usually necessary.

Asparaginase

Powder for injection: 10 000 IU in vial.

Also known as Crisantaspase.

Asparaginase is a complementary list cytotoxic medicine.

Uses: acute lymphoblastic leukaemia.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; **interactions:** Appendix 1.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Bleomycin

Powder for injection: 15 mg (as sulfate) in vial.

Bleomycin is a complementary list cytotoxic medicine.

Uses: adjunct to surgery and radiotherapy in palliative treatment of Hodgkin and non-Hodgkin lymphomas; reticulum cell sarcoma and lymphoma; carcinomas of the head, neck, larynx, cervix, penis, skin, vulva, testicles; embryonal cell carcinoma, choriocarcinoma, and teratoma; malignant effusions.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; renal impairment (Appendix 4); **interactions:** Appendix 1.

NOTE. Irritant to tissues.

Dose:

Consult specialist literature.

NOTE. Doses of bleomycin are expressed in international units. 1 Bleomycin Unit in the USP is equivalent to 1000 international units.

Adverse effects: see note above and consult specialist literature.

Calcium folinate

Injection: 3 mg/ml in 10-ml ampoule.
Tablet: 15 mg.

Calcium folinate is a complementary list medicine.

Uses: antidote in high-dose methotrexate therapy (as a 'folate rescue'); inadvertent overdose of methotrexate; palliative treatment of advanced metastatic colorectal cancer (in combination with fluorouracil).

Precautions: not for pernicious anaemia or other megaloblastic anaemias due to vitamin B_{12} deficiency; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Antidote to methotrexate (usually started 24 hours after administration of methotrexate), *by intramuscular* or *intravenous injection* or *by intravenous infusion*, **ADULT** and **CHILD,** up to 120 mg in divided doses over 12–24 hours, then 12–15 mg by *intramuscular injection,* or 15 mg *by mouth* every 6 hours for 48–72 hours.

Methotrexate overdosage (started as soon as possible, preferably within 1 hour of administration of methotrexate), *by intravenous injection* or *infusion*, **ADULT** and **CHILD**, dose equal to or higher than that of methotrexate, at rate not exceeding 160 mg/minute.

Colorectal cancer (in combination with fluorouracil), consult specialist literature.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

NOTE. Intrathecal injection of calcium folinate is contraindicated.

Adverse effects: allergic reactions; pyrexia after parenteral administration.

Chlorambucil

Tablet: 2 mg.

Chlorambucil is a complementary list cytotoxic medicine.

Uses: chronic lymphocytic leukaemia; some non-Hodgkin lymphomas; Hodgkin disease, and Waldenstrom (primary) macroglobulinaemia.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; renal impairment (Appendix 4); severe hepatic impairment (Appendix 5); **interactions:** Appendix 1.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Cisplatin

Powder for injection: 10 mg; 50 mg in vial.

Cisplatin is a complementary list cytotoxic medicine.

Uses: metastatic testicular tumours, metastatic ovarian tumours, advanced bladder carcinoma and other solid tumours, including lung, cervical, and head and neck cancers.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; renal impairment (Appendix 4); **interactions:** Appendix 1.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Cyclophosphamide

Powder for injection: 500 mg in vial.
Tablet: 25 mg.

Cyclophosphamide is a complementary list cytotoxic medicine.

Uses: malignant lymphomas including non-Hodgkin lymphomas, lymphocytic lymphoma and Burkitt lymphoma; multiple myeloma; leukaemias, mycosis fungoides; neuroblastoma; adenocarcinoma of the ovary; retinoblastoma; breast cancer.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; renal impairment (Appendix 4) and hepatic impairment (Appendix 5); **interactions:** Appendix 1.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Cytarabine

Powder for injection: 100 mg in vial.

Cytarabine is a complementary cytotoxic medicine.

Uses: acute lymphoblastic leukaemia; chronic myeloid leukaemia; meningeal leukaemia; erythroleukaemia; non-Hodgkin lymphomas.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; hepatic impairment (Appendix 5); **interactions:** Appendix 1.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Dacarbazine

Powder for injection: 100 mg in vial.

Dacarbazine is a complementary list cytotoxic medicine.

Uses: metastatic malignant melanoma; Hodgkin disease.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; renal impairment (Appendix 4); hepatic impairment (Appendix 5); **interactions:** Appendix 1.

NOTE. Irritant to tissues.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Dactinomycin

Powder for injection: 500 micrograms in vial.

Also known as Actinomycin D.

Dactinomycin is a complementary list cytotoxic medicine.

Uses: trophoblastic tumours, Wilm tumour, Ewing sarcoma, rhabdomyosarcoma.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; **interactions:** Appendix 1.

NOTE. Irritant to tissues.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Daunorubicin

Powder for injection: 50 mg (as hydrochloride).

Daunorubicin is a complementary cytotoxic medicine.

Uses: acute leukaemias.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; renal impairment (Appendix 4); hepatic impairment (Appendix 5); **interactions:** Appendix 1.

NOTE. Irritant to tissues.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Doxorubicin

Powder for injection: 10 mg; 50 mg (hydrochloride) in vial.

Doxorubicin hydrochloride is a complementary cytotoxic medicine.

Uses: acute leukaemias; carcinomas of the breast, bladder, ovary and thyroid; neuroblastoma; Wilm tumour; non-Hodgkin and Hodgkin lymphomas; soft tissue sarcomas, osteosarcoma.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; hepatic impairment (Appendix 5); **interactions:** Appendix 1.

NOTE. Irritant to tissues.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Etoposide

Capsule: 100 mg.

Injection: 20 mg/ml in 5-ml ampoule.

Etoposide is a complementary cytotoxic medicine.

Uses: refractory testicular tumours; lung cancer.

Contraindications: see note above and consult specialist literature; severe hepatic impairment (Appendix 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; renal impairment (Appendix 4); **interactions:** Appendix 1.

NOTE. Irritant to tissues.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Fluorouracil

Injection: 50 mg/ml in 5-ml ampoule.

Also known as 5-fluorouracil or 5FU.

Fluorouracil is a complementary list cytotoxic medicine.

Uses: carcinomas of the colorectum, breast, stomach, pancreas, cervix, prostate, ovary; and endometrium; liver tumours; head and neck tumours; actinic keratosis (section 13.5).

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; hepatic impairment (Appendix 5); **interactions:** Appendix 1.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Mercaptopurine

Tablet: 50 mg.

Mercaptopurine is a complementary list cytotoxic medicine.

Uses: acute leukaemias; inflammatory bowel disease (section 17.3).

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; renal impairment (Appendix 4); hepatic impairment (monitor liver function; see also Appendix 5); **interactions:** Appendix 1.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Methotrexate

Tablet: 2.5 mg (as sodium salt).
Powder for injection: 50 mg (as sodium salt) in vial.

Methotrexate is a complementary list cytotoxic medicine.

Uses: carcinoma of the breast, head and neck, and lung; trophoblastic tumours; acute lymphoblastic leukaemia, meningeal leukaemia; non-Hodgkin lymphomas; advanced cases of mycosis fungoides; non-metastatic osteosarcoma; severe rheumatoid arthritis (section 2.4); Crohn disease (section 17.3).

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; renal impairment (Appendix 4); hepatic impairment (Appendix 5); **interactions:** Appendix 1.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Procarbazine

Capsule: 50 mg (as hydrochloride).

Procarbazine is a complementary list cytotoxic medicine.

Uses: part of MOPP regimen in Hodgkin and non-Hodgkin lymphomas.

Contraindications: see note above and consult specialist literature; severe renal impairment (Appendix 4); severe hepatic impairment (Appendix 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3).

Precautions: see note above and consult specialist literature; **interactions:** Appendix 1.

Dose:

Consult specialist literature.

Adverse effects: see note above and consult specialist literature.

Vinblastine

Powder for injection: 10 mg (sulfate) in vial.

Vinblastine is a complementary list cytotoxic medicine.

Uses: disseminated Hodgkin and non-Hodgkin lymphomas; advanced testicular carcinoma, breast carcinoma; palliative treatment of Kaposi sarcoma; trophoblastic tumours; Letterer-Siwe disease.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3); intrathecal injection.

Precautions: see note above and consult specialist literature; hepatic impairment (Appendix 5); **interactions:** Appendix 1.

NOTE. Irritant to tissues.

Dose:

Consult specialist literature.

NOTE. Vinblastine is for **intravenous administration only**. Intrathecal injection causes severe neurotoxicity which is usually fatal.

Adverse effects: see note above and consult specialist literature.

Vincristine

Powder for injection: 1 mg; 5 mg (sulfate) in vial.

Vincristine is a complementary list cytotoxic medicine.

Uses: acute lymphoblastic leukaemia; neuroblastoma, Wilm tumour, Hodgkin and non-Hodgkin lymphomas; rhabdomyosarcoma, Ewing sarcoma; mycosis fungoides.

Contraindications: see note above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3); intrathecal injection.

Precautions: see note above and consult specialist literature; hepatic impairment (Appendix 5); **interactions:** Appendix 1.

NOTE. Irritant to tissues.

Dose:

Consult specialist literature.

NOTE. Vincristine is for **intravenous administration only**. Intrathecal injection causes severe neurotoxicity which is usually fatal.

Adverse effects: see note above and consult specialist literature.

8.3 Hormones and antihormones

The corticosteroids **prednisolone**, **dexamethasone** and **hydrocortisone** are synthetic hormones which may be given at pharmacological doses for certain malignancies, particularly haematological malignancies. Although there is no evidence for therapeutic superiority, prednisolone is used more commonly than dexamethasone or hydrocortisone (section 3); prednisolone is an important component of curative regimens for lymphomas and childhood leukaemias and for other cancers it has a palliative role. However, chronic use leads to the development of a cushingoid syndrome. For further information on the long-term use of corticosteroids, including the disadvantages, see section 18.1.

Tamoxifen is an estrogen-receptor antagonist. It is the adjuvant hormonal treatment of choice for all women with estrogen-receptor-positive breast cancer and for palliative management in patients with advanced disease. When given at the recommended doses, it has few adverse effects, although it can induce uterine endometrial malignancies.

Dexamethasone

Injection: 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule.

Dexamethasone is a complementary list medicine for the treatment of malignant neoplasms (section 3.3).

Hydrocortisone

Powder for injection: 100 mg (as sodium succinate) in vial.

Hydrocortisone is a complementary list medicine for the treatment of malignant neoplasms (section 3.3).

Prednisolone

Tablet: 5 mg; 25 mg.

Prednisolone is a representative corticosteroid with mainly glucocorticoid activity. Various drugs can serve as alternatives.

Prednisolone is a complementary list medicine for the treatment of malignant neoplasms.

Uses: with antineoplastic drugs for acute lymphoblastic and chronic lymphocytic leukaemias, Hodgkin disease, and non-Hodgkin 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 amoebiasis, strongyloidiasis, or tuberculosis possibly reactivated; increased severity of viral infections, particularly chickenpox 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 4); hepatic impairment (Appendix 5); diabetes mellitus; osteoporosis; glaucoma, corneal perforation; severe psychosis, epilepsy; psoriasis; peptic ulcer; hypothyroidism; history of steroid myopathy; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Leukaemias 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, oesophageal ulceration, development of or aggravation of peptic ulcers, abdominal distension, acute pancreatitis; increased appetite and weight gain; adrenal suppression with high doses, leading to cushingoid symptoms (moon face, acne, bruising, abdominal striae, truncal obesity, muscle wasting); menstrual irregularities and amenorrhoea; hypertension; osteoporosis, with resultant vertebral collapse and long-bone fractures; avascular osteonecrosis; ophthalmic effects including glaucoma, subcapsular cataracts, exacerbation of viral or fungal eye infections; diabetes mellitus; thromboembolism;

delayed tissue healing; myopathy, muscle weakness of arms and legs; depression, psychosis, epilepsy; raised intracranial pressure; hypersensitivity reactions.

Tamoxifen

Tablet: 10 mg; 20 mg (as citrate).

Tamoxifen is a complementary medicine for the treatment of breast cancer.

Uses: adjuvant treatment of estrogen-receptor-positive breast cancer; metastatic breast cancer.

Contraindications: pregnancy (exclude before treatment and advise non-hormonal contraception if appropriate, see also Appendix 2).

Precautions: monitor for endometrial changes (increased incidence of hyperplasia, polyps, cancer, and uterine sarcoma); cystic ovarian swellings in premenopausal women; increased risk of thromboembolism when used with antineoplastic drugs; breastfeeding (Appendix 3); avoid in porphyria; **interactions:** Appendix 1.

Dose:

Breast cancer, *by mouth*, **ADULT,** 20 mg daily.

Adverse effects: hot flushes; endometrial changes (symptoms such as vaginal bleeding and other menstrual irregularities, vaginal discharge, pelvic pain require immediate investigation); increased pain and hypercalcaemia with bony metastases; tumour flare; nausea and vomiting; liver enzyme changes (rarely cholestasis, hepatitis, hepatic necrosis); hypertriglyceridaemia (sometimes with pancreatitis); thromboembolic events; decreased platelet count; oedema; alopecia; rash; headache; visual disturbances including corneal changes, cataracts, retinopathy; rarely interstitial pneumonitis, and hypersensitivity reactions including angioedema, Stevens-Johnson syndrome, and bullous pemphigoid.

8.4 Medicines used in palliative care

NOTE. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends that all the drugs mentioned in *Cancer pain relief: with a guide to opioid availability*, 2nd ed. Geneva: WHO 1996 be considered essential. These drugs are included in the relevant sections of the Model List according to their therapeutic use, for example, analgesics.

Palliative care includes both pain relief and the symptomatic relief of conditions including dyspnoea, restlessness and confusion, anorexia,

constipation, pruritus, nausea and vomiting, and insomnia. Health organizations should be encouraged to develop their own palliative care services.

Pain relief can be achieved with drugs and neurosurgical, psychological, and behavioural 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 (see below). 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.

Pain management with analgesics

In the majority of patients, cancer pain can be relieved with analgesics:

- **By mouth:** if possible analgesics should be given by mouth. Rectal suppositories are useful in patients with dysphagia, uncontrolled vomiting or gastrointestinal obstruction. Continuous subcutaneous infusion offers an alternative route.
- **By the clock:** analgesics are more effective in preventing pain than relieving established pain, and therefore doses should be given at fixed time intervals and titrated against the patient's pain; if pain occurs between doses, a rescue dose should be given, and the next dose increased.
- **By the ladder:** the first step is to give a non-opioid analgesic such as **acetylsalicylic acid**, **paracetamol** or **ibuprofen**, if necessary with an adjuvant drug. If this does not relieve the pain, an opioid for mild to moderate pain, such as codeine, should be added. When this combination fails to relieve pain, an opioid for moderate to severe pain, such as morphine, should be substituted (section 2.2).
- **For the individual:** there are no standard doses for opioid drugs. The range for oral morphine is from as little as 5 mg to more than 100 mg every 4 hours. Sustained-release morphine tablets are available to enable oral dosing every 12 hours (section 2.2).
- **With attention to detail:** the first and last doses of the day should be linked to the patient's waking time and bedtime. Ideally the drug regimen should be written out in full for the patient and his or her family. The patient should be warned about possible adverse effects.

Medicines for neuropathic pain

Neuropathic pain often responds to a tricyclic antidepressant, such as **amitriptyline** (section 24.2), or to an anticonvulsant such as **carbamazepine** or **valproic acid** (both section 5); **ketamine** (section 1.1) or **lidocaine** (section 1.2) 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:
Antiparkinsonism 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. Dyskinesias 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 [not on the 15th WHO Model List]. Supplementary use of amantadine [not on the 15th WHO Model List], bromocriptine or the monoamine-oxidase-B inhibitor, selegiline [not on the 15th WHO Model List] 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. It can be treated with beta-blockers such as propranolol (120 mg daily) (section 7.2) 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 three 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 including 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 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.

Tetrabenazine [not included on the 15th WHO Model List], the dopamine-depleting drug, is used to control movement disorders in Huntington chorea and related disorders.

TICS. Tics which resemble choreiform movements are commonly associated with anxiety. However, in the more complex multiple tic disorder, Tourette syndrome, treatment with antipsychotic drugs may be required.

TARDIVE DYSKINESIA. It 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.

Biperiden

Injection: 5 mg (lactate) in 1-ml ampoule.
Tablet: 2 mg (hydrochloride).

Uses: drug-induced extrapyramidal symptoms (but not tardive dyskinesias) and adjunctive treatment of parkinsonism.

Contraindications: angle-closure glaucoma; untreated urinary retention; prostatic hypertrophy; myasthenia gravis; gastrointestinal obstruction.

Precautions: the elderly; cardiovascular disease, hepatic impairment (Appendix 5); renal impairment (Appendix 4); avoid abrupt withdrawal; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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.

Levodopa + carbidopa

Tablet: 100 mg + 10 mg; 250 mg + 25 mg.

Carbidopa is a representative peripheral dopa-decarboxylase inhibitor. Various medicines can serve as alternatives.

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, haematological, psychiatric, cardiovascular, and renal function required in long-term therapy; the elderly; avoid rapid dose increases; warn patients to resume normal activities gradually; avoid abrupt withdrawal; pregnancy (toxicity in animals) (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1.

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.

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Medicines affecting the blood

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10.1 Antianaemia medicines

Iron-deficiency anaemia

Anaemia occurs when the blood haemoglobin concentration falls below the normal range for the age and sex of the individual. It has many different aetiologies and thus it is essential that a correct diagnosis is made before initiating therapy. Any serious underlying cause of iron-deficiency anaemia, 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 haemodialysis patients.

Supplementation with iron and folic acid is recommended by WHO for all pregnant women; in addition, where prevalence of anaemia is above 40%, it is recommended that women of child-bearing age and breastfeeding 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 between 6 and 23 months if their diet does not include foods fortified with iron or if prevalence of anaemia 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 anaemia 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 anaemia in adults should be in the range, 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 haemoglobin concentration should rise by about 100–200 mg/100 ml per day *or* by 2 g/100 ml over 3–4 weeks. After the haemoglobin 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 faecal impaction. Oral iron may exacerbate diarrhoea 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) [not included on the 15th WHO Model List] or iron sucrose (a complex of ferric hydroxide with sucrose) [not included on the 15th WHO Model List] 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 haemodialysis (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 haemodialysis the haemoglobin response is not significantly faster with the parenteral route than the oral route.

Megaloblastic anaemias

Megaloblastic anaemias result from a lack of either vitamin B_{12} (hydroxocobalamin) or folate or both. The clinical features of folate-deficient megaloblastic anaemia are similar to those of vitamin B_{12} 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 B_{12} deficiency whether due to dietary deficiency or malabsorption (including pernicious anaemia). Pernicious anaemia is due to a lack of intrinsic factor, which is essential for vitamin B_{12} absorption.

Folate deficiency due to poor nutrition, pregnancy, use of antiepileptics, or malabsorption is treated with **folic acid**. Folic acid should not, however, be administered without vitamin B_{12} in undiagnosed megaloblastic anaemia because of the risk of precipitating neurological changes due to the underlying vitamin B_{12} deficiency.

Preparations containing a **ferrous salt and folic acid** are used for the prevention of megaloblastic anaemia in pregnancy. The low doses of folic acid

in these preparations are inadequate for the treatment of megaloblastic anaemias.

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 antiepileptic medication should be counselled by their doctor before starting folic acid (see also section 5).

Ferrous salt

Oral liquid: equivalent to 25 mg iron (as sulfate)/ml.
Tablet: equivalent to 60 mg iron.

Uses: iron-deficiency anaemia.

Contraindications: haemosiderosis, haemochromatosis; any form of anaemia not caused by iron deficiency; patients receiving repeated blood transfusions; parenteral iron therapy.

Precautions: should not be administered for longer than 6 months; pregnancy; peptic ulcer, regional enteritis, ulcerative colitis, intestinal strictures, diverticula; **interactions:** Appendix 1.

NOTE: Overdosage: see section 4.2.

Dose:

Iron-deficiency anaemia, *by mouth*, **ADULT,** elemental iron, 100–200 mg daily in divided doses.

Prevention of iron-deficiency anaemia (in those at particular risk), *by mouth*, **ADULT** (woman), elemental iron 60 mg daily; **CHILD** under 5 years, elemental iron, 2 mg/kg daily (maximum, 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 discolour stools. Liquid preparations containing iron salts should be well diluted

with water (and if possible swallowed through a drinking straw to prevent discoloration of the teeth).

Adverse effects: constipation, diarrhoea, dark stools, nausea, epigastric pain, gastrointestinal irritation; long-term or excessive administration may cause haemosiderosis.

Ferrous salt + folic acid

Tablet: equivalent to 60 mg iron + 400 micrograms folic acid.

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 anaemia; overdosage: see section 4.2; **interactions:** Appendix 1.

Dose:

Severe anaemia, *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 salt.

Folic acid

Tablet: 1 mg; 5 mg.

Uses: treatment of folate-deficiency megaloblastic anaemia; prevention of neural tube defects in pregnancy.

Contraindications: should never be given without vitamin B_{12} in undiagnosed megaloblastic anaemia or other vitamin B_{12} deficiency states because of the risk of precipitating subacute combined degeneration of the spinal cord; folate-dependent malignant disease.

Precautions: women receiving antiepileptic therapy (need counselling before starting folic acid, see also note above); **interactions:** Appendix 1.

Dose:

Treatment of folate-deficiency, megaloblastic anaemia, *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

Injection: 1 mg in 1-ml ampoule.

Uses: megaloblastic anaemias due to vitamin B_{12} deficiency.

Precautions: except in emergencies, should not be given before diagnosis confirmed; monitor serum potassium levels (arrhythmias secondary to hypokalaemia in early therapy).

Dose:

Megaloblastic anaemia 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 anaemias, *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; hypokalaemia during initial treatment.

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 (section 12.5), the management of unstable angina (section 12.9), 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 haemorrhage 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.

Oral anticoagulants take at least 48–72 hours for the anticoagulant effect to develop fully; if an immediate effect is needed, heparin must be given concomitantly (see above). **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 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 haemorrhage. Prothrombin time should be checked on a daily basis initially, and then at longer intervals depending on response.

If severe haemorrhage 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 6th 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 haemorrhage, 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.

Haemophilia

Desmopressin [not included on the 15th WHO Model List] by injection may aid haemostasis and be useful in mild forms of haemophilia. For minor procedures, including dental surgery, it may circumvent the need for factor VIII. For the use of factor VIII and factor IX in haemophilia, see section 11.2.

Heparin sodium

Injection: 1000 IU/ml; 5000 IU/ml; 20 000 IU/ml in 1-ml ampoule.

Uses: treatment and prophylaxis of deep-vein thrombosis and pulmonary embolism; unstable angina (section 12.1); ischaemic stroke (section 12.5).

Contraindications: hypersensitivity to heparin; haemophilia and other haemorrhagic disorders, thrombocytopenia, peptic ulcer, recent cerebral haemorrhage, severe hypertension, severe liver or renal disease; after major trauma or recent surgery (especially to eye or nervous system); acute bacterial endocarditis.

Precautions: hepatic impairment (Appendix 5); renal failure (Appendix 4); the elderly; hypersensitivity to low molecular weight heparins; spinal or epidural anaesthesia (risk of spinal haematoma); pregnancy (Appendix 2); diabetes mellitus, acidosis, concomitant potassium-sparing drugs (increased risk of hyperkalaemia); **interactions:** Appendix 1.

Dose:

Treatment of deep-vein thrombosis and pulmonary embolism, *by intravenous injection*, **ADULT,** loading dose of 5000 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; *by intravenous injection*, **SMALL ADULT** and **CHILD**,

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,** 5000 IU 2 hours before surgery, then every 8–12 hours for 7 days or until patient is ambulant (monitoring not needed); **PREGNANT WOMAN,** 5000–10,000 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); haemorrhage, skin necrosis, hypersensitivity reactions including urticaria, angioedema, and anaphylaxis; osteoporosis after prolonged use and rarely alopecia.

Phytomenadione

Injection: 10 mg/ml in 5-ml ampoule.
Tablet: 10 mg.

Uses: antagonist to warfarin; treatment and prophylaxis against haemorrhagic disease of the newborn.

Precautions: elderly (reduce dose); hepatic impairment (Appendix 5); not an antidote to heparin; pregnancy (Appendix 2); **interactions:** Appendix 1.

Dose:

Warfarin-induced hypoprothrombinaemia; no bleeding or minor bleeding, *by slow intravenous injection*, **ADULT,** 500 micrograms or *by mouth*, **ADULT,** up to 5 mg; moderate haemorrhage, *by mouth* or *by intramuscular injection*, **ADULT,** 10–20 mg; severe haemorrhage, **ADULT**, *by slow intravenous injection*, 5–10 mg.

Treatment of haemorrhagic disease of the newborn, *by intravenous* or *intramuscular injection*, **NEONATE,** 1 mg, with further doses if necessary at 8-hour intervals.

Prophylaxis of haemorrhagic 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 breastfed babies a third dose after 1 month.

Adverse effects: hypersensitivity reactions including flushing, dyspnoea, 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).

Protamine sulfate

Injection: 10 mg/ml in 5-ml ampoule.

Uses: antidote to overdosage 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, dyspnoea, allergic reactions including angioedema and anaphylaxis.

Warfarin

Tablet: 1 mg; 2 mg; 5 mg (sodium salt).

Warfarin is a representative oral anticoagulant. Various medicines can serve as alternatives.

Uses: prophylaxis of embolization in rheumatic heart disease and atrial fibrillation; prophylaxis of thrombi formation after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient ischaemic attacks (section 12.5).

Contraindications: pregnancy (see note above and Appendix 2); peptic ulcer, severe hypertension, bacterial endocarditis.

Precautions: hepatic impairment (Appendix 5); renal failure (Appendix 4), recent surgery, breastfeeding (Appendix 3); avoid cranberry juice (risk of potentiating anticoagulant effect); **interactions:** Appendix 1.

Dose:

NOTE. Wherever possible, the base-line prothrombin time (INR) should be determined before the initial dose is given.

Prophylaxis and treatment of thromboembolic disorders, *by mouth*, **ADULT,** usual induction dose, 10 mg daily for 2 days, according to the individual patient; the subsequent dose depends upon the prothrombin time; the usual daily maintenance dose, 3–9 mg daily taken at the same time each day.

Adverse effects: haemorrhage; hypersensitivity, rash, alopecia, diarrhoea, unexplained drop in haematocrit, "purple toes", skin necrosis, jaundice, hepatic dysfunction, nausea, vomiting, pancreatitis.

SECTION 11:
Blood products and plasma substitutes

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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 (section 26.2).

In medical emergencies, there is usually an existing fluid deficit which 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 hyponatraemia, especially following illness or injury which increase the secretion of antidiuretic hormones (section 26.2).

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 (Solutions correcting water, electrolyte, and acid–base disturbances).

11.1 Plasma substitutes

Dextran 70 and polygeline [not included on the 15th WHO Model List] are macromolecular substances which are metabolized slowly; they may be used to expand and maintain blood volume in shock arising from conditions such as burns or septicaemia. 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 haemorrhage 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

Injectable solution: 6%.

Dextran is a representative plasma substitute. Various preparations can serve as alternatives (polygeline, 3.5% solution for injection is considered equivalent).

Uses: short-term blood volume expansion.

Contraindications: severe congestive heart failure; renal failure; bleeding disorders such as thrombocytopenia and hypofibrinogenaemia.

Precautions: cardiac disease, liver disease (Appendix 5), renal impairment (Appendix 4); monitor urine output; avoid haematocrit 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 2).

Dose:

Short-term blood volume expansion, *by rapid intravenous infusion*, **ADULT,** 500–1000 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 haemostasis; 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 haemophilia. Bleeding episodes in haemophilia require prompt treatment with replacement therapy. **Factor VIII**, used for the treatment of haemophilia 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 haemophilia 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 haemophilia 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 which 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

Dried.

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.

Uses: replacement therapy for factor IX deficiency in haemophilia B; bleeding due to deficiencies of factors II, VII, or X.

Contraindications: disseminated intravascular coagulation.

Precautions: risk of thrombosis (probably less risk with highly purified preparations).

Dose:

Haemophilia 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 VIII concentrate

Dried.

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.

Uses: control of haemorrhage in haemophilia A.

Precautions: intravascular haemolysis after large or frequently repeated doses in patients with blood groups A, B, or AB (less likely with high potency, highly purified concentrates).

Dose:

Haemophilia A, *by slow intravenous infusion*, **ADULT** and **CHILD,** according to patient's needs.

Adverse effects: allergic reactions including chills, fever.

Human normal immunoglobulin

Intramuscular administration: 16% protein solution.

Intravenous administration: 5%; 10% protein solution.

Normal immunoglobulin

Normal immunoglobulin solution is administered by intravenous infusion for primary immunodeficiencies and immunomodulation in autoimmune disease including Guillain-Barré syndrome and Kawasaki disease. Solutions for intramuscular and subcutaneous injection are used for primary immune deficiency. Normal immunoglobulin should be used in hospital settings where specialist supervision is available.

Normal immunoglobulin (human, polyvalent)

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.

NOTE. Formulations from different manufacturers vary and should not be regarded as equivalent; consult individual manufacturer's product literature.

Uses: replacement therapy in primary immunodeficiency, Kawasaki disease.

Precautions: monitor vital signs; **interactions:** Appendix 1.

Dose:

NOTE. National recommendations may vary. Consult individual manufacturer's product literature for dose and administration recommendations for specific diseases; recommended doses may vary from those listed below.

Replacement therapy in primary immunodeficiencies: Initial loading intravenously in divided doses until serum IgG level is > 6 g/l. Maintenance doses by intravenous, subcutaneous or intramuscular routes: normally 0.4 – 0.8 g/kg/month for children and adults. Dose to be titrated depending on inter-current infections or trough serum IgG level. Intravenous doses may be given at one, two, 3 or 4 week intervals. Subcutaneous doses may be given at 1, 2, 3 , 4 or 7 day intervals.

For immunomodulation in autoimmune conditions: Maximum recommended dose is 2g/kg over at least 48 hours. Depending on specific autoimmune disease: 0.4 g/kg/day for 5 days or 0.8-1 g/kg the first day and repeated once if indicated.

ADMINISTRATION. Infusion rates of less than 8 g per hour are recommended. Immunoglobulin should be administered under the supervision of an immunologist or other experienced physician. In general, this should be in a hospital with adequate facilities for monitoring the infusion as well as the condition for which it is being administered, until the patient is stable, at which point treatment at home can be considered after formal training in an expert centre.

Adverse effects: nausea, vomiting, headache (may develop 24 hours after infusion); dizziness, dry mouth, chills, sweating, hypothermia, fever, eczema, rash, urticaria, hypotension, wheezing; anaphylactoid reactions also reported; with immunomodulatory doses also immune haemolysis, aseptic meningism, increased plasma viscosity, hypercoagulopathy, and renal impairment.

SECTION 12:
Cardiovascular medicines

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12.1 Antianginal 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 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 antianginal 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 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 $beta_2$ (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 hyperglycaemia or they can enhance the hypoglycaemic effect of insulin and may precipitate hypoglycaemia.

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 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 ischaemia; if beta-blockers are contraindicated, **verapamil** is an alternative, provided left ventricular function is adequate (see also section 12.5).

Prinzmetal angina

Treatment is similar to that for unstable angina, except that a calcium-channel blocker is used instead of a beta-blocker.

Atenolol

Tablet: 50 mg; 100 mg.

Atenolol is a representative beta-adrenoceptor antagonist (beta-blocker). Various medicines can serve as alternatives.

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 angina, marked bradycardia, hypotension, sick sinus syndrome, second- and third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with an alpha-blocker).

Precautions: avoid abrupt withdrawal especially in ischaemic heart disease; history of obstructive airway disease (use with caution and monitor lung function (see also Contraindications above); pregnancy (Appendix 2) and breastfeeding (Appendix 3); first-degree atrioventricular block; portal hypertension (liver function deteriorates); renal impairment (reduce dose; Appendix 4); diabetes mellitus (small decrease in glucose tolerance, which can mask symptoms of hypoglycaemia); history of hypersensitivity [increased reaction to allergens, also reduced response to epinephrine (adrenaline)]; myasthenia gravis; **interactions:** Appendix 1.

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, diarrhoea, constipation, and abdominal cramp; fatigue; cold hands and feet;

exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances including nightmares; depression, confusion; hypoglycaemia or hyperglycaemia; exacerbation of psoriasis; rash, dry eyes, and oculomucocutaneous syndrome (reversible on withdrawal) rarely reported.

Glyceryl trinitrate

Tablet (sublingual): 500 micrograms.

NOTE. Glyceryl trinitrate tablets are unstable. They should therefore be dispensed in glass or stainless steel containers, and closed with a foil-lined cap which 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; hypovolaemia; hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia; head trauma; cerebral haemorrhage; angle-closure glaucoma.

Precautions: severe hepatic impairment (Appendix 5); renal impairment (Appendix 4); hypothyroidism; malnutrition; hypothermia; recent history of myocardial infarction; **interactions:** Appendix 1.

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 dinitrate

Tablet (sublingual): 5 mg.

Isosorbide dinitrate is a representative nitrate vasodilator. Various drugs can serve as alternatives.

Uses: prophylaxis and treatment of angina; heart failure (section 12.4).

Contraindications: hypersensitivity to nitrates; hypotension; hypovolaemia; hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia; head trauma; cerebral haemorrhage; angle-closure glaucoma.

Precautions: severe hepatic impairment (Appendix 5); renal impairment (Appendix 4); hypothyroidism; malnutrition; hypothermia; recent history of myocardial infarction; **interactions:** Appendix 1.

TOLERANCE. Patients taking isosorbide dinitrate for the long-term management of angina may often develop tolerance to the antianginal effect; this can be avoided by giving the second of 2 daily doses of longer-acting oral presentations after an 8-hour rather than a 12-hour interval, thus ensuring a nitrate-free interval each day.

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 (see advice on Tolerance above).

Adverse effects: throbbing headache; flushing; dizziness, postural hypotension; tachycardia; paradoxical bradycardia also reported.

Verapamil

Tablet: 40 mg; 80 mg (hydrochloride).

NOTE. Sustained-release (prolonged-release) tablets are available. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation.

Uses: angina, including stable, unstable, and Prinzmetal; 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 5); children (specialist advice only); pregnancy (Appendix 2) and breastfeeding (Appendix 3); avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 1.

Dose:

Angina, *by mouth*, **ADULT,** 80–120 mg 3 times daily (120 mg 3 times daily usually required in Prinzmetal angina).

Adverse effects: constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, and ankle oedema; rarely allergic reactions including pruritus, urticaria, angioedema, and erythema multiforme (Stevens-Johnson syndrome); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; gynaecomastia and gingival hyperplasia on long-term treatment; hypotension, heart failure, bradycardia, heart block, and asystole (due to negative inotropic effect) with high doses.

12.2 Antiarrhythmic 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.

Antiarrhythmics 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 hypokalaemia. When antiarrhythmic 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** (section 12.1) or a calcium-channel blocker such as **verapamil** (section 12.1). **Digoxin**, a cardiac glycoside, slows the ventricular response and is particularly appropriate if atrial fibrillation is accompanied by congestive heart failure (see also section 12.4). 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 (section 10.2) is preferred to acetylsalicylic acid (section 12.5) in preventing emboli. If atrial fibrillation began within the previous 48 hours, and there does not appear to be a danger of thromboembolism, antiarrhythmic 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, antiarrhythmics 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.

Torsades de pointes is a special form of ventricular tachycardia associated with prolongation of the QT interval; it may be congenital but is often drug-induced. Initial treatment with intravenous infusion of magnesium sulfate (usual dose, 2 g over 10–15 minutes, repeated once if necessary) together with temporary pacing is usually effective. Prolonged QT interval may be treated with a beta-adrenoceptor antagonist beta-blocker (but *not* sotalol) and pacing; antiarrythmic drugs (including lidocaine) should be avoided because they can further prolong the QT interval.

Bradyarrhythmias

Sinus bradycardia (less than 50 beats/minute) 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

Tablet: 50 mg; 100 mg.

Atenolol is a representative beta-adrenoceptor antagonist (beta-blocker). Various drugs can serve as alternatives.

Uses: arrhythmias; angina and mycocardial infarction (section 12.1); 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 angina, marked bradycardia, hypotension, sick sinus syndrome, second- and third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with an alpha-blocker).

Precautions: avoid abrupt withdrawal especially in ischaemic heart disease; history of obstructive airway disease (use with caution and monitor lung function; see also Contraindications above); pregnancy (Appendix 2) and breastfeeding (Appendix 3); first-degree atrioventricular block; portal hypertension (liver function deteriorates); renal impairment (reduce dose; Appendix 4); diabetes mellitus (small decrease in glucose tolerance, which can mask symptoms of hypoglycaemia); history of hypersensitivity [increased reaction to allergens, also reduced response to epinephrine (adrenaline)]; myasthenia gravis; **interactions:** Appendix 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: gastrointestinal disturbances including nausea, vomiting, diarrhoea, constipation, and abdominal cramp; fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances including nightmares; depression, confusion; hypoglycaemia or hyperglycaemia; exacerbation of psoriasis; rare reports of rash, dry eyes and oculomucocutaneous syndrome (reversible on withdrawal) rarely reported.

Digoxin

Injection: 250 micrograms/ml in 2-ml ampoule.
Oral liquid: 50 micrograms/ml.
Tablet: 62.5 micrograms; 250 micrograms.

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; the elderly (reduce dose); renal impairment (Appendix 4); avoid hypokalaemia; avoid rapid intravenous administration (nausea and increased risk of arrhythmias); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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, diarrhoea, and abdominal pain; visual disturbances, headache, fatigue, drowsiness, confusion, dizziness, delirium, hallucinations, depression; arrhythmias, heart block; rarely rash, and intestinal ischaemia; gynaecomastia on long-term use; thrombocytopenia reported.

Epinephrine (adrenaline)

Injection: 100 micrograms/ml (as acid tartrate or hydrochloride) in 10-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 labour; **interactions:** Appendix 1.

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 hyperglycaemia also reported; in overdosage arrhythmias, cerebral haemorrhage, and pulmonary oedema.

Lidocaine

Injection: 20 mg (hydrochloride)/ml in 5-ml ampoule.

Uses: ventricular arrhythmias (especially after myocardial infarction); local anaesthesia (section 1.2).

Contraindications: sinoatrial disorder, any grade of atrioventricular block or any other type of conduction disturbances, severe myocardial depression, acute porphyria or hypovolaemia.

Precautions: lower dosage in congestive heart failure and following cardiac surgery; bradycardia; hepatic impairment (Appendix 5); severe respiratory depression; the elderly; pregnancy (Appendix 2); and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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/minute, followed immediately *by intravenous infusion* of 1–4 mg/minute, 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, paraesthesia, drowsiness, confusion, apnoea, 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 overdosage); hypersensitivity reactions also reported.

Procainamide

Injection: 100 mg (hydrochloride)/ml in 10-ml ampoule.

Procainamide is a representative antiarrhythmic drug. Various drugs can serve as alternatives.

Procainamide is also a complementary list medicine for use when drugs on the core WHO Model List are known to be ineffective or inappropriate for a given patient.

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: the elderly, renal impairment (Appendix 4); hepatic impairment (Appendix 5); asthma, myasthenia gravis, pregnancy (Appendix 2); breastfeeding (Appendix 3); use only under specialist supervision; **interactions:** Appendix 1.

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/minute, with ECG monitoring; may be repeated at 5-minute intervals until arrhythmia controlled; maximum 1 g.

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/minute; if further antiarrhythmic 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, diarrhoea, anorexia, rash, pruritus, urticaria, flushing, fever, myocardial depression, heart failure, angioedema, depression, dizziness, psychosis; blood disorders including leukopenia, haemolytic anaemia and agranulocytosis after prolonged treatment; lupus erythematosus-like syndrome; high plasma procainamide concentration may impair cardiac conduction.

Quinidine

Tablet: 200 mg (sulfate).

Quinidine is a representative antiarrhythmic drug. Various medicines can serve as alternatives.

Quinidine is also a complementary list antiarrhythmic medicine for use when drugs on the core WHO Model List cannot be made available.

NOTE. Quinidine sulfate, 200 mg or quinidine bisulfate, 250 mg.

Uses: suppression of supraventricular arrhythmias and ventricular arrhythmias; maintenance of sinus rhythm after cardioversion of atrial fibrillation.

Contraindications: complete heart block.

Precautions: partial heart block; extreme care in uncompensated heart failure, myocarditis, and severe myocardial damage; myasthenia gravis; acute infections or fever (symptoms may mask hypersensitivity reaction to quinidine; administer an initial test dose to exclude hypersensitivity); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Initial test dose, *by mouth,* **ADULT,** 200 mg.

Arrhythmias, *by mouth*, **ADULT,** 200–400 mg 3–4 times daily, with frequent ECG monitoring; increased if necessary in supraventricular tachycardia to 600 mg every 2–4 hours (maximum, 3–4 g daily).

Adverse effects: hypersensitivity reactions, nausea, vomiting, diarrhoea, rash, anaphylaxis, purpura, pruritus, urticaria, fever, thrombocytopenia, agranulocytosis after prolonged treatment, psychosis, angioedema, hepatotoxicity, respiratory difficulties; cardiac effects including myocardial depression, heart failure, ventricular arrhythmias, and hypotension; cinchonism including tinnitus, impaired hearing, vertigo, headache, visual disturbances, abdominal pain, and confusion; lupus erythematosus-like syndrome.

Verapamil

Injection: 2.5 mg (hydrochloride)/ml in 2-ml ampoule.
Tablet: 40 mg; 80 mg (hydrochloride).

NOTE. Sustained-release (prolonged-release) tablets are available. A proposal to include such a product in a national list of essential drugs should be supported by adequate documentation.

Uses: supraventricular arrhythmias; angina (section 12.1); 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); hepatic impairment (Appendix 5); children (specialist advice only);

pregnancy (Appendix 2) and breastfeeding (Appendix 3); avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 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: constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, and ankle oedema; rarely allergic reactions including pruritus, urticaria, angioedema, and Erythema multiforme (Stevens-Johnson syndrome); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; gynaecomastia and gingival hyperplasia on long-term treatment; hypotension, heart failure, bradycardia, heart block, and asystole (due to negative inotropic effect) with high doses.

12.3 Antihypertensive medicines

Management of hypertension

Treatment of hypertension should be integrated into a programme 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, 160–179 mmHg systolic and 100–109 mmHg diastolic and Grade 3 hypertension, 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.

Lifestyle changes should be introduced for all patients; they include weight reduction, reduction in alcohol intake, reduction of dietary sodium, stopping tobacco smoking, and reduction in saturated fat intake. The patient should eat a healthy nutritious diet including adequate fruit and vegetables and should exercise regularly. These measures alone may be sufficient in mild hypertension, but patients with moderate to severe hypertension will also require specific antihypertensive therapy.

Drug treatment of hypertension

There are no significant differences between the major groups of antihypertensive drugs in terms of efficacy, side-effects, and quality of life although some differences in response are seen which are related to age or ethnic group. Therefore, 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.

In the absence of compelling indications for another class of drug, thiazide diuretics, such as **hydrochlorothiazide** (see also section 16), 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 (see section 12.1); 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 inhibitors (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 (section 5) is the treatment of choice to prevent eclamptic convulsions in eclampsia and severe pre-eclampsia.

Amlodipine

Tablet: 5 mg.

Amlodipine is a representative dihydropyridine calcium-channel blocker. Various drugs can serve as alternatives.

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 5); pregnancy (Appendix 2); and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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, oedema; headache, dizziness, sleep disturbances, fatigue; less commonly gastrointestinal disturbances, dry mouth, taste disturbances, hypotension, syncope, chest pain, dyspnoea, rhinitis, mood changes, tremor, paraesthesia, increased sweating, urinary disturbances, impotence, gynaecomastia, 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, hyperglycaemia, thrombocytopenia, peripheral neuropathy, angioedema, and urticaria.

Atenolol

Tablet: 50 mg; 100 mg.

Atenolol is a representative beta-adrenoceptor antagonist (beta-blocker). Various drugs can serve as alternatives.

Uses: hypertension; angina (section 12.1); arrhythmias (section 12.2); 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 angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree atrioventricular block, cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma (unless used with an alpha-blocker).

Precautions: avoid abrupt withdrawal especially in ischaemic heart disease; history of obstructive airway disease (use with caution and monitor lung function; see also Contraindications above); pregnancy (Appendix 2) and breastfeeding (Appendix 3); first-degree atrioventricular block; portal hypertension (liver function deteriorates); reduce dose in renal impairment (reduce dose; Appendix 4); diabetes mellitus (small decrease in glucose tolerance, masking of symptoms of hypoglycaemia); history of hypersensitivity [increased reaction to allergens, also reduced response to epinephrine (adrenaline)]; myasthenia gravis; **interactions:** Appendix 1.

Dose:

Hypertension, *by mouth*, **ADULT,** 50 mg once daily (higher doses rarely necessary).

Adverse effects: gastrointestinal disturbances including nausea, vomiting, diarrhoea, constipation, and abdominal cramp; fatigue; cold hands and feet; exacerbation of intermittent claudication and Raynaud phenomenon; bronchospasm; bradycardia, heart failure, conduction disorders, hypotension; sleep disturbances including nightmares; depression, confusion; hypoglycaemia or hyperglycaemia; exacerbation of psoriasis; rash, dry eyes, and oculomucocutaneous syndrome (reversible on withdrawal) rarely reported.

Enalapril

Tablet: 2.5 mg.

Enalapril is a representative angiotensin-converting enzyme (ACE) inhibitor. Various medicines can serve as alternatives.

Uses: hypertension; heart failure (section 12.4).

Contraindications: hypersensitivity to ACE inhibitors (including angioedema); renovascular disease; pregnancy (Appendix 2).

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; see also Appendix 4); hepatic impairment (Appendix 5); possibly increased risk of agranulocytosis in collagen vascular disease; history of idiopathic or hereditary angioedema (use with care or avoid); breastfeeding (Appendix 3); **interactions:** Appendix 1.

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 (may not be possible in heart failure due to the risk of pulmonary oedema). 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 polyacrilonitrile 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, diarrhoea, 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 syndrome, angioedema, bronchospasm, rhinorrhoea, dry mouth, sore throat, pulmonary infiltrates, paraesthesia, vertigo, nervousness, depression, confusion, drowsiness, insomnia, dream abnormalities, pruritus, urticaria, alopecia, flushing, impotence, gynaecomastia, 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

Powder for injection: 20 mg (hydrochloride) in ampoule.
Tablet: 25 mg; 50 mg (hydrochloride).

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, porphyria.

Precautions: hepatic impairment (Appendix 5); renal impairment (reduce dose; Appendix 4); coronary artery disease (may provoke angina; avoid after myocardial infarction until stabilized); cerebrovascular disease; pregnancy (Appendix 2) and breastfeeding (Appendix 3); occasionally over-rapid blood pressure reduction even with low parenteral doses; **interactions:** Appendix 1.

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/minute; usual maintenance dose 50–150 micrograms/minute.

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, diarrhoea, 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, paraesthesia, arthralgia, myalgia, increased lacrimation, dyspnoea; raised plasma creatinine, proteinuria, haematuria; blood disorders including haemolytic anaemia, leukopenia, and thrombocytopenia.

Hydrochlorothiazide

Tablet (scored): 25 mg.

Hydrochlorothiazide is a representative thiazide diuretic. Various medicines can serve as alternatives.

Uses: alone in mild hypertension, and in combination with other drugs in moderate to severe hypertension; heart failure (section 12.4); oedema (section 16).

Contraindications: severe renal or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease.

Precautions: renal impairment (Appendix 4); hepatic impairment (Appendix 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3); the 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 1.

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;

hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis, hypercalcaemia; hyperglycaemia, hyperuricaemia, 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 oedema, and severe skin reactions.

Methyldopa

Tablet: 250 mg.

Uses: hypertension in pregnancy.

Contraindications: depression; active liver disease; phaeochromocytoma, porphyria.

Precautions: history of hepatic impairment (Appendix 5); renal impairment (Appendix 4); blood counts and liver-function tests advised; history of depression; positive direct Coomb test in up to 20% of patients (affects blood cross-matching); interference with laboratory tests; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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, lightheadedness, postural hypotension, weakness, fatigue, headache, fluid retention and oedema, sexual dysfunction; impaired concentration and memory, depression, mild psychosis, disturbed sleep and nightmares; drug fever, influenza-like syndrome; nausea, vomiting, constipation, diarrhoea, dry mouth, stomatitis, sialadenitis; liver function impairment, hepatitis, jaundice, rarely fatal hepatic necrosis; bone marrow depression, haemolytic anaemia, leukopenia, thrombocytopenia, eosinophilia; parkinsonism; rash including toxic epidermal necrolysis; nasal congestion; black or sore tongue; bradycardia, exacerbation of angina; myalgia, arthralgia, paraesthesia, Bell palsy; pancreatitis; hypersensitivity reactions including lupus erythematosus-like syndrome, myocarditis, pericarditis; gynaecomastia, hyperprolactinaemia, amenorrhoea; urine darkens on standing.

Sodium nitroprusside

Powder for infusion: 50 mg in ampoule.

Sodium nitroprusside is a complementary list medicine for the treatment of hypertensive crisis.

Uses: hypertensive crisis (when treatment by mouth is not possible).

Contraindications: severe hepatic impairment; compensatory hypertension; severe vitamin B_{12} deficiency; Leber optic atrophy.

Precautions: impaired pulmonary function; hypothyroidism; renal impairment (Appendix 4); ischaemic heart disease, impaired cerebral circulation; hyponatraemia; raised intracranial pressure; the elderly; hypothermia; monitor blood pressure and blood cyanide concentration; monitor blood thiocyanate concentration if given for more than 3 days; avoid sudden withdrawal (reduce infusion over 15–30 minutes to avoid rebound effects); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions**: Appendix 1.

Dose:

Hypertensive crisis, *by intravenous infusion*, **ADULT,** initially 0.3–1.5 micrograms/kg/minute, increased gradually to 0.5–6 micrograms/kg/minute; (lower doses in patients already being treated with antihypertensives); maximum, 8 micrograms/kg/minute; stop infusion if response is unsatisfactory after 10 minutes at the maximum dose.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: severe hypotension; adverse effects associated with over-rapid reduction in blood pressure include headache, dizziness; retching, abdominal pain; perspiration; palpitations, apprehension, retrosternal discomfort; rarely reduced platelet count, and acute transient phlebitis; adverse effects associated with excessive concentrations of cyanide metabolite include tachycardia, sweating, hyperventilation, arrhythmias, and marked metabolic acidosis (discontinue infusion and give sodium nitrite followed by sodium thiosulfate (see section 4.2).

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 oedema 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. Hypokalaemia 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 oedema. 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 hypokalaemia.

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 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 [not included on the 15th WHO Model List], 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 (see also section 12.2) 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 dilatation, which reduces left ventricular preload, leading to a reduction in pulmonary congestion and dyspnoea. **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 per minute) cause vasoconstriction, with a worsening of heart failure.

Digoxin

Injection: 250 micrograms/ml in 2-ml ampoule.
Oral liquid: 50 micrograms/ml.
Tablet: 62.5 micrograms; 250 micrograms.

Uses: heart failure; supraventricular arrhythmias (section 12.2).

Contraindications: hypertrophic obstructive cardiomyopathy (unless also severe 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; the elderly (reduce dose); renal impairment (Appendix 4); avoid hypokalaemia; avoid rapid intravenous administration (nausea and increased risk of arrhythmias); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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. 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, diarrhoea, abdominal pain; visual disturbances, headache, fatigue, drowsiness, confusion, dizziness, delirium, hallucinations, depression; arrhythmias, heart block; rarely rash, and intestinal ischaemia; gynaecomastia on long-term use; thrombocytopenia reported.

Dopamine

Injection: 40 mg (hydrochloride)/ml in 5-ml vial.

Dopamine is a complementary list medicine for inotropic support.

Uses: cardiogenic shock including in myocardial infarction and cardiac surgery.

Contraindications: tachyarrhythmia, ventricular fibrillation; ischaemic heart disease; phaeochromocytoma; hyperthyroidism.

Precautions: correct hypovolaemia before, and maintain blood volume during the treatment; correct hypoxia, hypercapnia, and metabolic acidosis before or at same time as starting treatment; use low dose in cardiogenic shock due to myocardial infarction; history of peripheral vascular disease (increased risk of ischaemia of extremities); breastfeeding (Appendix 3); the elderly; **interactions:** Appendix 1.

Dose:

Cardiogenic shock, *by intravenous infusion* into a large vein, **ADULT,** initially 2–5 micrograms/kg/minute, gradually increased by 5–10 micrograms/kg/minute according to blood pressure, cardiac output, and urine output (seriously ill patients, up to 20–50 micrograms/kg/minute).

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, dyspnoea; hypertension particularly in overdosage.

Enalapril

Tablet: 2.5 mg.

Enalapril is a representative angiotensin-converting enzyme (ACE) inhibitor. Various medicines can serve as alternatives.

Uses: heart failure (with a diuretic); prevention of symptomatic heart failure in patients with left ventricular dysfunction; hypertension (section 12.3).

Contraindications: hypersensitivity to ACE inhibitors (including angioedema); renovascular disease; pregnancy (Appendix 2).

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; see also Appendix 4); hepatic impairment (Appendix 5); possibly increased risk of agranulocytosis in collagen vascular disease; history of idiopathic or hereditary angioedema (use with care or avoid); breastfeeding (Appendix 3); **interactions:** Appendix 1.

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 (may not be possible in heart failure due to the risk of pulmonary oedema). 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 polyacrilonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; also withhold before desensitization with wasp or bee venom.

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: dizziness, headache; less commonly, nausea, diarrhoea, 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 syndrome, angioedema, bronchospasm, rhinorrhoea, dry mouth, sore throat, pulmonary infiltrates, paraesthesia, vertigo, nervousness, depression, confusion, drowsiness, insomnia, dream abnormalities, pruritus, urticaria, alopecia, flushing, impotence, gynaecomastia, 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.

Furosemide

Injection: 10 mg/ml in 2-ml ampoule.
Tablet: 40 mg.

See Section 16.

Hydrochlorothiazide

Tablet (scored): 25 mg.

Hydrochlorothiazide is a representative thiazide diuretic. Various medicines can serve as alternatives.

Uses: heart failure; hypertension (section 12.3); oedema (section 16).

Contraindications: severe renal or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease.

Precautions: renal impairment (Appendix 4); hepatic impairment (Appendix 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3); the elderly (reduce dose); 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 1.

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: 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; hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis, hypercalcaemia; hyperglycaemia, hyperuricaemia, gout; rash, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible); blood disorders including neutropenia, and thrombocytopenia; pancreatitis, intrahepatic cholestasis; acute renal failure; hypersensitivity reactions including pneumonitis, pulmonary oedema, and severe skin reactions.

12.5 Antithrombotic medicines

Anticoagulants such as heparin sodium and warfarin prevent thrombus formation or the extension of an existing thrombus. For further details, see section 10.2 (Medicines affecting coagulation). 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 comprises two phases:

1. initial management of the acute attack;
2. 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 ischaemia; 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 ischaemic 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 antiarrhythmic drug **lidocaine** (section 12.2) should be given.

All patients should be closely monitored for hyperglycaemia; 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 ischaemic or haemorrhagic; 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 ischaemic stroke. Prophylaxis in patients at risk of ischaemic stroke includes antiplatelet drugs such as **acetylsalicylic acid** or oral anticoagulants such as warfarin (section 10.2). Treatment of acute ischaemic 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). Long-term therapy with acetylsalicylic acid reduces the risk of having another stroke.

Antiplatelet drugs are **not** used in the management of haemorrhagic 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 one 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

Tablet: 100 mg.

Uses: acute myocardial infarction, acute ischaemic stroke, prophylaxis of cerebrovascular disease or myocardial infarction; pyrexia, pain, inflammation (section 2.1); migraine (section 7.1).

Contraindications: hypersensitivity (including asthma, angioedema, urticaria, or rhinitis) to acetylsalicylic acid or any other NSAIM; children and adolescents under 16 years (risk of Reye syndrome; see section 2.1); active peptic ulceration; haemophilia and other bleeding disorders.

Precautions: asthma; uncontrolled hypertension; pregnancy (Appendix 2) and breastfeeding (Appendix 3); see also section 2.1; **interactions:** Appendix 1.

Dose:

Prophylaxis of cerebrovascular disease or myocardial infarction, *by mouth*, **ADULT,** 75–100 mg daily.

Treatment of acute myocardial infarction, acute ischaemic stroke, *by mouth,* **ADULT,** 150–300 mg.

Adverse effects: bronchospasm; gastrointestinal haemorrhage (rarely major), also other haemorrhage (for example, subconjunctival); see also section 2.1.

Streptokinase

Powder for injection: 1.5 million IU in vial.

Streptokinase is a complementary drug; it is used in the management of myocardial infarction and thromboembolism.

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 haemorrhage, surgery (including dental), parturition, trauma; heavy vaginal bleeding; haemorrhagic 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, oesophageal 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 2); 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 haemorrhage); 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 haemorrhage 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 hypertriglyceridaemia. 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. **Simvastatin** is a representative example of this class of drugs; others include pravastatin, lovastatin, fluvastatin, and atorvastatin [not included on the 15th WHO Model List]. 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.

Simvastatin

Tablet: 5 mg; 10 mg; 20 mg; 40 mg.

Simvastatin is a representative statin. Various medicines can serve as alternatives.

Uses: prevention of cardiovascular events in patients with high cardiovascular risk due to atherosclerotic cardiovascular disease or diabetes mellitus.

Contraindications: active liver disease (or persistently abnormal liver function tests); porphyria; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions: history of liver disease or a high alcohol intake (use should be avoided in active liver disease; Appendix 5); monitor liver function at initiation of treatment, at 12 weeks after (or if dose increased), and at 6-month intervals thereafter (discontinue if serum transaminase concentration rises to, and persists at, 3 times the upper limit of the reference range); hypothyroidism (see Muscle effects below); increased risk of myopathy or rhabdomyolysis (patients should be advised to report unexplained muscle pain; see Muscle effects below); renal impairment (Appendix 4); avoid grapefruit juice; **interactions:** Appendix 1.

Dose:

Prevention of cardiovascular events, *by mouth*, **ADULT,** initially 20–40 mg once daily at night, adjusted at intervals of at least 4 weeks (maximum, 80 mg once daily at night).

NOTE. Maximum simvastatin dose with concomitant ciclosporin, danazol, fibrate or lipid-lowering dose of nicotinic acid, 10 mg daily; with concomitant amiodarone or verapamil, 20 mg daily; with concomitant diltiazem, 40 mg daily.

MUSCLE EFFECTS. Discontinue simvastatin if myopathy is suspected and creatine kinase is elevated (more than 5 times upper limit of normal), or if severe muscular symptoms are present. Simvastatin should not be started if creatine kinase is elevated in patients at high risk of muscle effects. There is an increased risk of myopathy if simvastatin is given at high dosage or with a fibrate, with lipid-lowering doses of nicotinic acid, or with immunosuppressants such as ciclosporin (monitor liver function, and creatine kinase in symptomatic patients). Risk of rhabdomyolysis (rare) may be increased in renal impairment and hypothyroidism.

Adverse effects: muscle effects including myalgia, myopathy, myositis, and rhabdomyolysis (see Muscle effects above); abdominal pain, flatulence, constipation, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis, raised serum transaminases, hepatitis, jaundice, headache, dizziness, asthenia, peripheral neuropathy, paresthesia, anaemia, pruritus, alopecia, rash, hypersensitivity reactions (including angioedema and anaphylaxis).

SECTION 13:
Dermatological medicines (topical)

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13.1 Antifungal medicines

Ringworm

Benzoic acid and methylrosanilinium chloride (gentian violet) (see section 13.2) 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 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 (section 6.3), 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 (see section 6.3).

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 (see section 6.3).

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 (section 6.3) 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 (section 13.2), and systemic antifungals may also be needed.

Nail infections (onychomycosis, tinea unguium) are difficult to treat; fingernails may require 6 months treatment with oral griseofulvin (section 13.2) 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).

Candidosis

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 of candida are now seen in patients with HIV infection.

Cutaneous candidosis usually responds to twice daily applications of creams containing either **miconazole** or **clotrimazole** (see section 6.3). 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 skins 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

Cream or ointment: 6% + 3%.

Also known as Whitfield ointment.

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.

Miconazole

Cream or ointment: 2% (nitrate).

Miconazole is a representative topical antifungal. Various drugs can serve as alternatives.

Uses: superficial fungal infections due to dermatophytes and yeasts, and secondary infections caused by Gram-positive cocci, including ringworm, intertrigo, candida napkin rash, paronychia, and pityriasis versicolor.

Administration:

Skin infections, **ADULT** and **CHILD,** *apply* directly to clean dry lesions twice daily, continuing for at least 10 days after the condition has cleared.

Nail infections, **ADULT** and **CHILD,** *apply* directly to the affected area 1–2 times daily.

Adverse effects: occasional local irritation and burning, also contact dermatitis; discontinue if sensitization occurs.

Selenium sulfide

Detergent-based suspension: 2%.

Selenium sulfide is a complementary drug for use in rare disorders or in exceptional circumstances.

Uses: pityriasis versicolor (lotion), seborrhoeic dermatitis [detergent-based suspension (section 13.3)].

Contraindications: children under 5 years.

Precautions: do not apply to damaged skin (risk of systemic toxicity); avoid contact with eyes; do not use within 48 hours of applying preparations for hair colouring, straightening, or permanent waving.

Administration:

Pityriasis versicolor, **ADULT** and **CHILD** 5 years and above, *apply* lotion with a small amount of water to the entire affected area and rinse off after 10 minutes, repeat once daily for 7–14 days; or *apply* undiluted lotion to the affected area at bedtime and rinse off the following morning, application repeat, 1–6 times over 2 weeks; repeat course if necessary.

Seborrhoeic dermatitis, **ADULT** and **CHILD** 5 years and above, *massage* 5–10 ml of shampoo into wet hair and leave for 2–3 minutes before rinsing thoroughly; repeat twice weekly for 2 weeks, then once weekly for 2 weeks, thereafter only when needed.

NOTE. To minimize absorption, rinse hair thoroughly after use and remove all traces from skin (including nails).

Adverse effects: local irritation, hair discoloration or loss; absorption may result in systemic toxicity including tremors, weakness, lethargy, pain in

lower abdomen, occasional vomiting (symptoms usually resolve within 10 days).

Sodium thiosulfate

Solution: 15%.

Uses: pityriasis versicolor; cyanide poisoning (section 4.2).

Administration:

Pityriasis versicolor, **ADULT** and **CHILD,** *apply* directly to the affected area twice daily for 4 weeks.

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 (section 15.1). Superficial crusts should be gently washed with soap and water or a weak solution of aluminium diacetate (section 13.4) 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% or fusidic acid 2% [neither are included on the 15th WHO Model List] can be used to treat bacterial infections of the skin such as impetigo and folliculitis. To prevent the development of resistance, mupirocin and fusidic acid 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 which 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 favouring the emergence of resistant organisms. Only widespread superficial or deep-seated skin infections associated with fever require treatment with a systemic antibiotic (sections 6.2.1 and 6.2.2).

Whenever possible, the choice of an antimicrobial should be based on the results of sensitivity tests.

Methylrosanilinium chloride (Gentian violet)

Aqueous solution: 0.5%.
Tincture: 0.5%.

Also known as gentian violet or crystal violet.

Methylrosanilinium chloride is a representative topical anti-infective drug. Various medicines can serve as alternatives.

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).

Neomycin sulfate + bacitracin

Ointment: 5 mg neomycin sulfate + 250 IU bacitracin zinc/g.

Bacitracin is a representative topical antibacterial. Various medicines can serve as alternatives.

Uses: superficial bacterial infections of the skin due to *staphylococci* and *streptococci.*

Contraindications: 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: sensitization, 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.

Potassium permanganate

Aqueous solution: 1:10 000.

NOTE. Potassium permanganate is sometimes supplied as an aqueous stock solution of 1 in 1000 (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).

Contraindications: avoid occlusive dressings.

Precautions: irritant to mucous membranes.

Administration:

Impetigo, **ADULT** and **CHILD,** *apply dressings* soaked in a 1:10 000 (0.01%) solution until superficial crusts can be gently separated.

Suppurating superficial wounds and tropical ulcers, **ADULT** and **CHILD,** *apply dressings* soaked in a 1:10 000 (0.01%) 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 (0.01%) solution every 8 hours.

Adverse effects: local irritation; skin and fabrics stained brown.

Silver sulfadiazine

Cream: 1%, in 500-g container.

Uses: prophylaxis and treatment of infection in burns.

Contraindications: hypersensitivity to sulfonamides; pregnancy (Appendix 2); neonates.

Precautions: renal impairment (Annex 4); hepatic impairment (Annex 5); G6PD deficiency; breastfeeding (Appendix 3).

Administration:

Infection in burns, **ADULT** and **CHILD,** *apply* using aseptic technique once daily (more frequently if volume of exudate is large) whilst 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.

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 oedema. 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 pruritis 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, which mainly occurs in infants and children; it is associated with intense itching, with areas of red skin. Pruritus may be partially relieved by applying astringent aluminium diacetate (section 13.4) 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 (section 6.2.2).

Seborrhoeic dermatitis

Use of a keratolytic shampoo and exposure to ultraviolet light reduce both the inflammation and the scaling resulting from seborrhoeic 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 (section 13.1), 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; see section 3); ciclosporin (see section 8.1) and retinoids [not included on the 15th WHO Model List] 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.

Betamethasone

Cream or ointment: 0.1% (as valerate).

Betamethasone is a representative potent topical corticosteroid. Various medicines can serve as alternatives.

Uses: severe inflammatory skin conditions including contact dermatitis, atopic dermatitis (eczema), seborrhoeic dermatitis, lichen planus, and intractable pruritus; psoriasis of the scalp, hands, and feet (section 13.5).

Contraindications: untreated skin infections, broken skin, rosacea, acne, perioral dermatitis.

Precautions: children (avoid prolonged use and use under specialist supervision); psoriasis (may precipitate severe pustular psoriasis on withdrawal; avoid in widespread plaque psoriasis); adrenal suppression if used on a large area of the body or for a long time, particularly with an occlusive dressing; avoid use on the face for more than 7 days; secondary infection requires treatment with an appropriate antimicrobial.

Administration:

Inflammatory skin conditions, **ADULT** and **CHILD** over 2 years of age, *apply* sparingly to the affected area, 1–2 times daily until improvement occurs, then less frequently.

Adverse effects: exacerbation of local infection; local atrophic changes (particularly on the face and in skinfolds), characterized by thinning of the dermis, depigmentation, dilatation of superficial blood vessels, and formation of striae; contact dermatitis; perioral dermatitis; acne at site of application; suppression of the hypothalamic–pituitary–adrenal axis with prolonged or widespread use (particularly under occlusion); hypertrichosis reported.

Calamine lotion

Lotion.

Calamine is a representative topical antipruritic. Various medicines can serve as alternatives.

Uses: mild pruritus.

Administration:

Mild pruritus, **ADULT** and **CHILD,** *apply* liberally to the entire affected area 3–4 times daily.

Hydrocortisone

Cream or ointment: 1% (acetate).

Hydrocortisone is a representative mild topical corticosteroid. Various medicines can serve as alternatives.

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 (section 13.5).

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.

13.4 Astringent medicines

Aluminium diacetate 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.

Aluminium diacetate

Solution: 5%.

Uses: wet dressings to assist healing of suppurating superficial wounds, tropical ulcers, and eczematous skin lesions; removal of adherent crusts.

Precautions: avoid use of plastic or rubber occlusive dressings.

Administration:

Impetigo and pemphigus, **ADULT** and **CHILD,** *apply dressings* soaked in 0.65% solution until superficial crusts can be separated.

Suppurating superficial wounds and tropical ulcers, **ADULT** and **CHILD,** *apply dressings* soaked in a 0.65% solution to the affected area for 30–120 minutes daily, changing dressings every 5–15 minutes; tropical ulcers also require treatment with procaine benzylpenicillin for 2–4 weeks (section 6.2.1).

DILUTION. Aluminium diacetate solution, 5% should be diluted before use, 1 part in 7.7 parts water, to give a 0.65% solution.

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 (section 18.4), antiandrogens, or retinoids [not included on the 15th WHO Model List]. 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 (section 6.2.2) 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.

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-inflammators.

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 [not included on the 15th WHO Model List]. A preparation containing **urea** (carbamide), 10%, which has moisturizing and keratolytic properties, may prove more effective than an emollient.

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 (section 13.3) may be used on the face and flexures, whereas a potent corticosteroid such as betamethasone (section 13.3) 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, sufficient 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 on the 15th WHO Model List], 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 of 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, or laser therapy are possible options.

Benzoyl peroxide

Cream or lotion: 5%.

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

Solution: 5%.

Uses: chronic psoriasis, either alone or in combination with exposure to ultraviolet light.

Contraindications: inflamed, broken or infected skin.

Precautions: 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 (UVB) rays, allowing at least 24 hours between exposure and treatment with coal tar.

Adverse effects: irritation, photosensitivity reactions; rarely hypersensitivity; skin, hair, and fabrics discoloured.

Dithranol

Ointment: 0.1-2%.

Uses: moderately severe psoriasis.

Contraindications: hypersensitivity; avoid use on face, acute eruptions, excessively inflamed areas.

Precautions: irritant (avoid contact with eyes and healthy skin).

Administration:

Psoriasis (initiate under medical supervision), **ADULT** and **CHILD,** starting with a lower strength preparation (0.1%), carefully *apply* directly to lesions only, leave in contact for 30 minutes, then wash off thoroughly; repeat application daily, gradually increasing strength to 2% and contact time to 60 minutes at weekly intervals; some 0.1–0.5% strength preparations are suitable for overnight use.

NOTE: Wash hands thoroughly after use.

Adverse effects: local irritation; excessive erythema or spread of lesions (discontinue use); conjunctivitis following contact with eyes; staining of skin, hair, and fabrics.

Fluorouracil

Ointment: 5%.

Uses: premalignant and malignant skin conditions, including actinic keratosis; malignant disease (section 8.2).

Contraindications: haemorrhagic ulcerated tissue.

Precautions: avoid mucous membranes and eyes; since ultraviolet light intensifies the inflammatory reaction, avoid prolonged exposure to sunlight.

Administration:

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 cm^2.

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.

Podophyllum resin

Solution: 10-25%.

Podophyllum resin is a representative antimitotic agent used to treat warts. Various medicines can serve as alternatives.

Uses: external anogenital warts; plantar warts.

Contraindications: pregnancy (Appendix 2) and breastfeeding (Appendix 3); children.

Precautions: avoid use on large areas; very irritant to eyes (keep away from face); avoid contact with normal skin, mucus membranes, and open wounds.

Administration:

Warts, **ADULT,** *apply* carefully to warts, avoiding contact with normal tissue; rinse off after 1–6 hours; may be repeated at weekly intervals but no more than 4 times in all; only few warts should be treated at any one time.

NOTE. Must be applied by a trained health-care professional.

Adverse effects: systemic effects resulting from cutaneous absorption include nausea, vomiting, abdominal pain and diarrhoea; also transient leukopenia and thrombocytopenia; renal failure; delayed neurotoxicity including visual and auditory hallucinations, delusions, disorientation, confusion, and delirium following excessive application.

Salicylic acid

Solution: 5%.

Uses: hyperkeratotic conditions, including warts; adjunct in treatment of psoriasis, ringworm (section 13.1), seborrhoeic 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.

NOTE. 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.

Urea

Cream or ointment: 10%.

Also known as Carbamide.

Uses: hydrating agent and keratolytic for dry, scaling and itching skin conditions, including mild psoriasis.

Precautions: avoid application to face or broken skin; avoid contact with eyes.

Administration:

Dry, scaling skin disorders, **ADULT** and **CHILD,** *apply* directly to the affected area twice daily, preferably to damp skin.

Adverse effects: transient stinging and local irritation.

13.6 Scabicides and pediculicides

Scabies

Scabies is caused by a mite, *Sarcoptes scabiei*, that 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 one week.

Ivermectin (section 6.1.2) in a single oral dose of 200 micrograms/kg may be used in combination with topical drugs for the treatment of hyperkeratotic scabies that does not respond to topical treatment alone.

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 *Pthirus pubis*, which may also affect the eye lashes 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, hair brushes and combs should also be disinfected.

Head and body lice are readily treated with **permethrin**; malathion [not included on the 15th WHO Model List] is effective against pubic lice. **Benzyl benzoate** may be used for all lice infestations.

Benzyl benzoate

Lotion: 25%.

Benzyl benzoate is a representative parasiticide. Various medicines can serve as alternatives.

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; breastfeeding (Appendix 3) (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.

Permethrin

Cream: 5%. Lotion: 1%.

Uses: scabies; head and body lice.

Precautions: do not use on inflamed or broken skin; avoid contact with eyes; breastfeeding (Annex 3) (withhold during treatment).

Administration:

Scabies and body lice, **ADULT** and **CHILD,** *apply* cream over whole body and wash off after 8–12 hours; if hands area washed 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 oedema.

SECTION 14:
Diagnostic agents

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14.1 Ophthalmic medicines

For general information on the use of eye drops, see section 21.

Fluorescein is used in ocular diagnostic procedures and for locating damaged areas of the cornea due to injury or disease.

Tropicamide is a short-acting relatively weak mydriatic that dilates the pupil and paralyses the ciliary muscle. It facilitates the examination of the fundus of the eye.

Fluorescein

Eye drops: 1% (sodium salt).

Uses: detection of lesions and foreign bodies in the eye.

Contraindications: avoid use with soft contact lenses.

Precautions: transient blurring of vision (see below).

SKILLED TASKS. Transient blurring of vision; advise patient not to operate machinery or drive until vision is clear.

Administration:

Detection of lesions and foreign bodies in the eye, *by ocular instillation*, **ADULT** and **CHILD,** instil sufficient solution dropwise to stain the damaged area.

Tropicamide

Eye drops: 0.5%.

Tropicamide is a representative mydriatic. Various medicines can serve as alternatives.

Uses: dilatation of the pupil to examine the fundus.

Precautions: hypermetropic (long-sighted) patients and patients aged over 60 years may precipitate acute angle-closure glaucoma); darkly pigmented iris (more resistant to pupillary dilatation; exercise caution to avoid overdosage).

SKILLED TASKS. Advise patient not to perform skilled tasks, for 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, hyperaemia, oedema, 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 which 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 artefacts. 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.

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

Injection: 140-420 mg iodine (as sodium or meglumine salt)/ml in 20-ml ampoule.

Meglumine amidotrizoate and sodium amidotrizoate are representative iodinated ionic monomeric radiocontrast media. Various media can serve as alternatives.

Uses: urography, venography, operative cholangiography, splenoportography, arthrography, diskography; computer-assisted axial tomography.

Contraindications: hypersensitivity to iodine-containing compounds.

Precautions: history of allergy, atopy, or asthma; severe hepatic impairment (Appendix 5); renal impairment (Appendix 4); dehydration (correct fluid and electrolyte balance before administration); multiple myeloma (risk of fatal renal failure if dehydrated); cardiac disease, hypertension, phaeochromocytoma, sickle-cell disease, hyperthyroidism, the elderly or debilitated patients, and children (increased risk of adverse effects); pregnancy (Appendix 2); breastfeeding (Appendix 3); may interfere with thyroid function tests; concomitant use of biguanides (withdraw 48 hours before administration; restart when renal function stabilized).

NOTE: Important: because of 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, diarrhoea, metallic taste, flushing, sensations of heat, weakness, dizziness, headache, cough, rhinitis, sweating, sneezing, lacrimation, visual disturbances, pruritus, salivary gland enlargement, pallor, cardiac disorders, haemodynamic disturbances and hypotension; disseminated intravascular coagulation; fibrinolysis and depression of blood coagulation factors; rarely nephrotoxicity, convulsions, paralysis, coma, rigors, arrhythmias, pulmonary oedema, 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

Aqueous suspension.

Uses: radiographic examination of the gastrointestinal tract.

Contraindications: intestinal obstruction, and/or conditions such as pyloric stenosis or lesions which 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.

Precautions: 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 diarrhoea, 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).

Iohexol

Injection: 140-350 mg iodine/ml in 5-ml; 10-ml; 20-ml ampoules.

Iohexol is a representative iodinated non-ionic radiocontrast medium. Various media can serve as alternatives.

Uses: urography, venography, angiography, ventriculography, operative cholangiography, splenoportography, arthrography, diskography; computer-assisted axial tomography.

Contraindications: hypersensitivity to iodine-containing compounds.

Precautions: history of allergy, atopy or asthma; severe hepatic impairment (Appendix 5); renal impairment (Appendix 4); dehydration (correct fluid and electrolyte balance before administration); multiple myeloma (risk of fatal renal failure if dehydrated); cardiac disease, hypertension,

phaeochromocytoma, sickle-cell disease, hyperthyroidism, the elderly or debilitated patients, and children (increased risk of adverse effects); pregnancy (Appendix 2); breastfeeding (Appendix 3); may interfere with thyroid-function tests; concomitant use of biguanides (withdraw 48 hours before administration; restart when renal function stabilized).

NOTE: **Important:** because of 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. Only by specialist radiographers, according to manufacturer's directions.

Adverse effects: nausea, vomiting, metallic taste, flushing, sensations of heat, weakness, dizziness, headache, cough, rhinitis, sweating, sneezing, lacrimation, visual disturbances, pruritus, salivary gland enlargement, pallor, cardiac disorders, haemodynamic disturbances and hypotension, nephrotoxicity; rarely convulsions, paralysis, coma, rigors, arrhythmias, pulmonary oedema, 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.

Meglumine iotroxate

Solution: 5-8 g iodine in 100-250 ml.

Meglumine iotroxate is a representative iodinated ionic dimeric radiocontrast medium. Various media can serve as alternatives. It is a complementary medicine.

Uses: examination of the gallbladder and biliary tract.

Contraindications: hypersensitivity to iodine-containing compounds.

Precautions: history of allergy, atopy or asthma; severe hepatic impairment (Appendix 5); renal impairment (Appendix 4); dehydration (correct fluid and electrolyte balance before administration); multiple myeloma (risk of fatal renal failure if dehydrated); cardiac disease, hypertension, phaeochromocytoma, sickle-cell disease, hyperthyroidism, the elderly or debilitated patients, and children (increased risk of adverse effects); pregnancy; breastfeeding; may interfere with thyroid-function tests; concomitant use of biguanides (withdraw 48 hours before administration; restart when renal function stabilized).

NOTE: **Important:** because of risk of hypersensitivity reactions, adequate resuscitation facilities must be immediately available during radiographic procedures.

Dose:

Examination of gallbladder and biliary tract, *by intravenous injection*, **ADULT,** 100 ml of meglumine iotroxate solution, 10.5% over at least 15 minutes (consult manufacturer's literature).

ADMINISTRATION. By specialist radiographers only, according to manufacturer's directions.

Adverse effects: nausea, vomiting, metallic taste, flushing, sensations of heat, weakness, dizziness, headache, cough, rhinitis, sweating, sneezing, lacrimation, visual disturbances, pruritus, salivary gland enlargement, pallor, cardiac disorders, haemodynamic disturbances and hypotension or hypertension; rarely, convulsions, paralysis, coma, rigors, arrhythmias, pulmonary oedema, 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.

SECTION 15:
Disinfectants and antiseptics

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15.2 Disinfectants 323

15.1 Antiseptics

An antiseptic is a type of disinfectant, which 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, venepuncture or surgical procedures. It is also used to disinfect hands and to clean surfaces.

Chlorhexidine

Solution: 5% (digluconate) for dilution.

Chlorhexidine is a representative disinfectant and antiseptic. Various agents can serve as alternatives.

Uses: antiseptic; disinfection of clean instruments.

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 (pre-operative 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.

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.

Ethanol

Solution: 70% (denatured).

Ethanol is a representative disinfectant and antiseptic. Various agents can serve as alternatives.

Uses: disinfection of skin prior to injection, venepuncture, or surgical procedures.

Precautions: flammable; avoid broken skin; patients have suffered severe burns when diathermy has been preceded by application of alcoholic skin disinfectants.

Administration:

Disinfection of skin, **ADULT** and **CHILD,** *apply* undiluted solution directly to the skin area.

Adverse effects: skin dryness and irritation with frequent application.

Polyvidone iodine

Solution: 10%.

Also known as Povidone–iodine.

Polyvidone iodine is a representative antiseptic. Various agents can serve as alternatives.

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 2) and breastfeeding (Appendix 3); broken skin (see below); renal impairment (Appendix 4).

LARGE OPEN WOUNDS. The application of polyvidone iodine to large wounds or severe burns may produce systemic adverse effects such as metabolic acidosis, hypernatraemia, and impairment of renal function.

Administration:

Pre- and post-operative 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 above).

Adverse effects: irritation of skin and mucous membranes; may interfere with thyroid function tests; systemic effects (see under Precautions).

15.2 Disinfectants

A disinfectant is a chemical agent, which 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, or 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, **chloroxylenol**, 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.

Chlorine base compound

Powder: (0.1% available chlorine) for solution.

Chlorine-releasing compounds are representative disinfectants. Various agents can serve as alternatives.

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.

Chloroxylenol

Solution: 4.8%.

Chloroxylenol is a representative disinfectant and antiseptic. Various agents can serve as alternatives.

Uses: antiseptic; disinfection of instruments and surfaces.

Precautions: aqueous solutions (which are susceptible to microbial contamination) should be freshly prepared; appropriate measures required to prevent contamination during storage or dilution.

Administration:

Antiseptic (wounds and other skin damage), *apply* a 1 in 20 dilution of 5% concentrate in water to the affected area.

Disinfection of instruments, *immerse* a 1 in 20 dilution of 5% concentrate in alcohol (70%).

DILUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: skin sensitivity reported.

Glutaral

Solution: 2%.

Uses: disinfection and sterilization of instruments and surfaces.

Precautions: minimize occupational exposure (adequate skin protection and measures to avoid inhalation of vapour).

Administration:

Disinfection of clean instruments, *immerse* in undiluted solution for 10–20 minutes; up to 3 hours may be required for certain instruments (for example, bronchoscopes with possible mycobacterial contamination); rinse with sterile water or alcohol after disinfection.

Sterilization of clean instruments, *immerse* in undiluted solution for up to 10 hours; rinse with sterile water or alcohol after disinfection.

Adverse effects: (occupational exposure) nausea, headache, airway obstruction, asthma, rhinitis, eye irritation, dermatitis, and skin discoloration.

SECTION 16:
Diuretics

Diuretics increase urinary excretion of water and electrolytes, and are therefore used to relieve oedema 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 oedema, 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 oedema due to left ventricular failure (see section 12.4). They are also used to treat oedema 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 *hypokalaemia* may be less with loop diuretics than with thiazide diuretics; if required, a potassium-sparing diuretic may be given as an adjunct to prevent hypokalaemia. Loop diuretics may cause *hypovolaemia* and excessive use can produce severe dehydration with the possibility of circulatory collapse. Furosemide may cause *hyperuricaemia* 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 that lasts 12–24 hours.

Thiazide diuretics are used in the management of oedema associated with mild to moderate congestive heart failure, renal dysfunction, or hepatic disease; however, thiazides are not effective in patients with poor renal function (i.e. a creatinine clearance of less than 30 ml per minute). 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 which may cause *hypokalaemia*; this is dangerous in patients with severe coronary artery disease and those being treated with cardiac glycosides. In hepatic failure, hypokalaemia can precipitate encephalopathy, particularly in alcoholic cirrhosis. Potassium-sparing diuretics are an effective alternative to potassium supplements for prevention of hypokalaemia 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 oedema 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 *hypokalaemia*. 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 *hypokalaemia* and of hypertension.

The most dangerous adverse effect of potassium-sparing diuretics, such as amiloride or spironolactone, is *hyperkalaemia*, which can be life-threatening. These diuretics are thus best avoided, or used with extreme caution, in patients who have or may develop hyperkalaemia, 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. *Hyponatraemia* is an adverse effect of all diuretics. The risk of *hypokalaemia*, 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 *hyperkalaemia*. Other electrolyte disturbances include *hypercalcaemia* (thiazides), *hypocalcaemia* (loop diuretics), and *hypomagnesaemia* (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.

Amiloride

Tablet: 5 mg (hydrochloride).

Uses: oedema associated with heart failure or hepatic cirrhosis (with ascites), usually in combination with thiazide or loop diuretic.

Contraindications: hyperkalaemia; renal failure.

Precautions: monitor electrolytes, particularly potassium; renal impairment (Appendix 4); diabetes mellitus; the elderly (reduce dose); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Oedema (used alone), *by mouth*, **ADULT,** initially 10 mg daily in 1 or 2 divided doses, adjusted according to response (maximum, 20 mg daily).

Oedema (in combination with a thiazide or a loop diuretic), *by mouth*, **ADULT,** initially 5 mg daily, increasing to 10 mg daily if necessary (maximum, 20 mg daily).

Adverse effects: hyperkalaemia, hyponatraemia (for other symptoms of fluid and electrolyte imbalance, see introductory notes above); diarrhoea, constipation, anorexia; paraesthesia, dizziness, minor psychiatric or visual disturbances; rash, pruritus; rise in blood urea nitrogen.

Furosemide

Injection: 10 mg/ml in 2-ml ampoule.
Tablet: 40 mg.

Furosemide is a representative loop diuretic. Various medicines can serve as alternatives.

Uses: oedema; 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; the elderly (reduce dose); pregnancy (Appendix 2); in oliguria, correct hypovolaemia before administration; renal impairment (Appendix 4), hepatic impairment (Appendix 5); prostatic enlargement; **interactions:** Appendix 1.

Dose:

Oedema, *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 oedema; **CHILD,** 1–3 mg/kg daily (maximum, 40 mg daily).

Acute pulmonary oedema, *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/minute; **CHILD,** 0.5–1.5 mg/kg daily (maximum, 20 mg daily)

Oliguria (glomerular filtration rate less than 20 ml/minute), *by slow intravenous infusion* at a rate not exceeding 4 mg/minute, **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 then, if there is no satisfactory response during the hour after the second dose, infuse 1 g over 4 hours; if there is no response after the third dose, dialysis is probably necessary; 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: hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis (for symptoms of fluid and electrolyte imbalance, see introductory notes), increased calcium excretion, hypovolaemia, hyperglycaemia (but less often than with thiazide diuretics); temporary increase in plasma cholesterol and triglyceride concentration; less commonly hyperuricaemia 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 taken).

Hydrochlorothiazide

Tablet (scored): 25 mg.

Hydrochlorothiazide is a representative thiazide diuretic. Various medicines can serve as alternatives.

Uses: oedema; diabetes insipidus; hypertension (section 12.3); heart failure (section 12.4).

Contraindications: severe renal or severe hepatic impairment; hyponatraemia, hypercalcaemia, refractory hypokalaemia, symptomatic hyperuricaemia; Addison disease.

Precautions: renal impairment (Appendix 4); hepatic impairment (Appendix 5); pregnancy (Appendix 2); breastfeeding (Appendix 3); the 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 1.

Dose:

Hypertension, *by mouth*, **ADULT,** 12.5 mg daily, increased to 25–50 mg daily if necessary.

Oedema, *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 oedema in patients unable to tolerate loop diuretics, *by mouth*, **ADULT,** up to 100 mg either daily or on alternate days (maximum, 100 mg daily).

Nephrogenic diabetes insipidus, *by mouth*, **ADULT,** initially up to 100 mg daily.

Adverse effects: hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis (for symptoms of fluid and electrolyte imbalance see introductory notes); hypercalcaemia; hyperglycaemia; hyperuricaemia, gout; rash, photosensitivity; altered plasma lipid concentration; rarely impotence (reversible), blood disorders including neutropenia and thrombocytopenia; pancreatitis, intrahepatic cholestasis; hypersensitivity reactions including pneumonitis, pulmonary oedema, and severe skin reactions; acute renal failure.

Mannitol

Injectable solution: 10%; 20%.

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 oedema, 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 oedema can be precipitated in patients with diminished cardiac reserve, and acute water intoxication may occur in patients with inadequate urine flow.

Uses: cerebral oedema; raised intraocular pressure (emergency treatment or before surgery).

Contraindications: pulmonary oedema; intracranial bleeding (except during craniotomy); severe congestive heart failure; metabolic oedema with abnormal capillary fragility; severe dehydration; renal failure (unless test dose produces diuresis).

Precautions: monitor fluid and electrolyte balance; monitor renal function.

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, re-evaluate 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 oedema, *by intravenous infusion* as a 20% solution infused rapidly, **ADULT** and **CHILD,** 1 g/kg.

PHARMACEUTICAL PRECAUTIONS. Solutions containing more than mannitol, 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 oedema (particularly in diminished cardiac reserve); chills, fever, chest pain, dizziness, visual disturbances; hypotension or hypertension; urticaria, hypersensitivity reactions; extravasation may cause oedema, skin necrosis, and thrombophlebitis; rarely acute renal failure (with large doses).

Spironolactone

Tablet: 25 mg.

Uses: refractory oedema in congestive heart failure; adjunct to ACE inhibitor and a loop or thiazide diuretic in severe congestive heart failure (see section 12.4); nephrotic syndrome; hepatic cirrhosis with ascites and oedema; ascites associated with malignancy; primary hyperaldosteronism.

Contraindications: hyperkalaemia; hyponatraemia; moderate renal impairment; Addison disease.

Precautions: monitor blood urea nitrogen and plasma electrolytes (discontinue if hyperkalaemia); the elderly (reduce dose); diabetes mellitus; renal impairment (Appendix 4); hepatic impairment (Appendix 5); pregnancy (Appendix 2) and breastfeeding (Appendix 3); porphyria; high doses carcinogenic in rodents; **interactions:** Appendix 1.

Dose:

Oedema, *by mouth*, **ADULT,** 100–200 mg daily, increased if necessary to 400 mg daily in resistant oedema; usual maintenance dose, 25–200 mg daily; **CHILD,** initially 1–3 mg/kg daily in 1–2 divided doses.

Primary hyperaldosteronism, *by mouth*, **ADULT**, diagnosis, 400 mg daily for 3–4 weeks (see note above).

Preoperative management, 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.

Adverse effects: hyperkalaemia, hyponatraemia, hyperchloraemic acidosis, dehydration (for symptoms of fluid and electrolyte imbalance, see introductory notes above); transient increase in blood urea nitrogen; diarrhoea; gynaecomastia, menstrual irregularities; impotence, hirsutism, deepening of voice; rash, ataxia, fever, hepatotoxicity.

SECTION 17:
Gastrointestinal medicines

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17.1 Antacids and other antiulcer medicines

Antacids (which usually contain aluminium or magnesium compounds) can often relieve symptoms in ulcer dyspepsia and in non-erosive gastro-oesophageal 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 H_2-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.

H_2-receptor antagonists (for example ranitidine) heal gastric and duodenal ulcers by reducing the secretion of gastric acid as a result of histamine H_2-receptor blockade; they can also relieve gastro-oesophageal reflux disease. High doses of H_2-receptor antagonists have been used in Zollinger–Ellison syndrome, but a proton-pump inhibitor is now preferred.

Maintenance treatment with low doses of H_2-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 the elderly who suffer ulcer complications.

Treatment of undiagnosed dyspepsia with H_2-receptor antagonists may be acceptable in younger patients but care is required in older people because their symptoms may be caused by gastric cancer.

H_2-receptor antagonist therapy can promote healing of NSAIM-associated ulcers (particularly duodenal). Treatment also reduces the risk of acid aspiration in obstetric patients at delivery (Mendelson syndrome).

Peptic ulcer

Peptic ulceration involves the stomach, duodenum, and lower oesophagus. 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 treatment with H_2-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 NSAIM 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 H_2-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") drug 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 three times daily for 1 week
plus
amoxicillin 500 mg three times daily for 1 week

The decision on choosing an 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 ulcerss

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 H_2-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 H_2-receptor antagonists concomitantly, but ulcers tend to heal more slowly with H_2-receptor antagonists if NSAIMs are continued. A proton pump inhibitor, such as omeprazole [not included on the 15th WHO Model List], is more effective but more expensive.

In patients who can discontinue NSAIM therapy after ulcer development, treatment with an H_2-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 H_2-receptor antagonists are often used to suppress gastric acid; *Helicobacter 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-oesophageal reflux disease

Gastro-oesophageal reflux disease (including non-erosive gastro-oesophageal reflux and erosive oesophagitis) is associated with a range of symptoms which include heartburn, acid regurgitation, and sometimes difficulty in swallowing (dysphagia); oesophageal inflammation (oesophagitis), ulceration, and stricture formation may occur and there is an association with asthma.

The management of gastro-oesophageal 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-oesophageal reflux disease, initial management may include the use of antacids. H_2-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 oesophagus), a short course of a proton pump inhibitor is needed initially.

Zollinger–Ellison syndrome

Management of Zollinger–Ellison syndrome requires high-dose H_2-receptor antagonist treatment. Although proton pump inhibitors are more effective than the H_2-receptor antagonists, particularly for cases resistant to other treatments, they are more expensive.

Aluminium hydroxide

Oral liquid: 320 mg/5 ml.
Tablet: 500 mg.

Uses: ulcer and non-ulcer dyspepsia; gastro-oesophageal reflux disease; hyperphosphataemia.

Contraindications: hypophosphataemia; undiagnosed gastrointestinal or rectal bleeding; appendicitis; porphyria.

Precautions: impaired renal function and renal dialysis (Appendix 4); hepatic impairment (Appendix 5); constipation; dehydration; fluid restriction; gastrointestinal disorders associated with decreased bowel motility or obstruction; **interactions:** Appendix 1.

Dose:

Dyspepsia, gastro-oesophageal reflux disease, *by mouth*, **ADULT,** 1–2 tablets chewed 4 times daily and at bedtime or 5–10 ml suspension 4 times daily, between meals and at bedtime; **CHILD** 6–12 years, 5 ml up to 3 times daily.

Hyperphosphataemia, *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); hypophosphataemia with increased bone resorption, hypercalciuria, and increased risk of osteomalacia (more common in patients on a low phosphate diet or on prolonged therapy); hyperaluminaemia resulting in osteomalacia, encephalopathy, dementia, and microcytic anaemia (in chronic renal failure treated with aluminium hydroxide as phosphate-binding agent).

Magnesium hydroxide

Oral liquid: equivalent to 550 mg magnesium oxide/10 ml.

Uses: ulcer and non-ulcer dyspepsia; gastro-oesophageal reflux disease.

Contraindications: severe renal impairment.

Precautions: renal impairment (Appendix 4); hepatic impairment (Appendix 5); **interactions:** Appendix 1.

Dose:

Dyspepsia, gastro-oesophageal reflux disease, *by mouth*, **ADULT,** 5–10 ml repeated according to patient's needs.

Adverse effects: diarrhoea; hypermagnesaemia 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).

Ranitidine

Injection: 25 mg/ml in 2-ml ampoule.
Oral liquid: 75 mg/5 ml.
Tablet: 150 mg (as hydrochloride).

Ranitidine is a representative H_2-receptor antagonist. Various medicines can serve as alternatives.

Uses: benign gastric and duodenal ulceration, gastro-oesophageal reflux disease, Zollinger–Ellison syndrome; other conditions where gastric acid reduction is beneficial.

Contraindications: porphyria.

Precautions: hepatic impairment (Appendix 5); renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); middle-aged or older patients and those whose symptoms change (may mask symptoms of gastric cancer); **interactions:** Appendix 1.

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 NSAIM-associated ulceration; in NSAIM-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 (maximum, 300 mg daily).

Benign gastric and duodenal ulceration, reflux oesophagitis, Zollinger–Ellison syndrome,
by intramuscular injection, **ADULT,** 50 mg every 6–8 hours;
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);
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 NSAIM-induced gastric or duodenal ulcer, *by mouth*, **ADULT,** 300 mg twice daily.

Gastro-oesophageal 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-oesophageal 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 labour, then every 6 hours.

Surgical procedures, *by intramuscular* or *slow intravenous injection*, **ADULT,** 50 mg 45–60 minutes before induction of anaesthesia (intravenous injection diluted to 20 ml and given over at least 2 minutes); *by mouth*, **ADULT,** 150 mg 2 hours before induction of anaesthesia, 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: diarrhoea and other gastrointestinal disturbances, headache, dizziness, rash, tiredness, acute pancreatitis, bradycardia, atrioventricular block, confusion, depression; rarely hallucinations (particularly in the elderly or the 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, gynaecomastia, and impotence; very rarely interstitial nephritis.

17.2 Antiemetic medicines

Metoclopramide has antiemetic 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; is also effective against radiation-induced nausea and vomiting. Combining metoclopramide with corticosteroids (such as dexamethasone) can improve its antiemetic effect in chemotherapy-induced nausea and vomiting (see also section 8.2). Metoclopramide may be useful in the management of gastro-oesophageal 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 D^2 dopaminergic blockade has pronounced histamine H^1 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.

Metoclopramide

Injection: 5 mg (hydrochloride)/ml in 2-ml ampoule.
Tablet: 10 mg (hydrochloride).

Uses: nausea and vomiting in gastrointestinal disorders, in migraine (section 7.1), and following surgery and treatment with cytotoxics (section 8.2) or radiotherapy; gastro–oesophageal reflux disease (section 17.1); 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, haemorrhage or perforation; 3–4 days after gastrointestinal surgery; convulsive disorders; phaeochromocytoma.

Precautions: the elderly, children and young adults; hepatic impairment (Appendix 5); renal impairment (Appendix 4); may mask underlying disorders such as cerebral irritation; avoid for 3–4 days after gastrointestinal surgery; pregnancy (Appendix 2) and breastfeeding (Appendix 3); Parkinson disease; epilepsy; depression; porphyria; **interactions:** Appendix 1.

Dose:

Nausea and vomiting, gastro-oesophageal 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 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 mg 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; see introductory note above); tardive dyskinesias on prolonged use; hyperprolactinaemia; drowsiness, restlessness, dizziness, headache, diarrhoea, depression, hypotension and hypertension reported; rarely neuroleptic malignant syndrome; rash, pruritus, oedema; cardiac conduction abnormalities following intravenous administration; rarely methaemoglobinaemia (more severe in G6PD deficiency).

Promethazine

Injection: 25 mg (hydrochloride)/ml in 2-ml ampoule.
Oral liquid: 5 mg (hydrochloride)/5 ml.
Tablet: 10 mg; 25 mg (hydrochloride).

Uses: management of postoperative and drug-induced nausea and vomiting; labyrinthine disorders, motion sickness; premedication (section 1.3).

Contraindications: porphyria; child under 2 years (risk of respiratory depression).

Precautions: prostatic hypertrophy; urinary retention; glaucoma; pyloroduodenal obstruction; hepatic disease (Appendix 5); epilepsy; the elderly and children (more susceptible to adverse effects); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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 (maximum, 100 mg in 24 hours).

Nausea and vomiting, *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 maximum, 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; extrapyramidal 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 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.

Treatment of acute attacks of ulcerative colitis and Crohn disease

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 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 disease unresponsive to other immunosuppressants.

Maintenance of remission

Sulfasalazine is most effective in the maintanance of remission of ulcerative colitis, but it is not so useful in Crohn 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 disease.

Additional treatments

Laxatives are required to facilitate bowel movement when proctitis is present. Antimotility drugs (such as codeine; section 17.5.3) and antispasmodic drugs should **not** be used in active ulcerative colitis because they can precipitate paralytic ileus and megacolon. Diarrhoea resulting from reduced bile salt absorption may improve with colestyramine [not included on the 15th WHO Model List]. General nutritional care and appropriate supplements are essential. High-fibre or low-residue diets should be used as appropriate. Irritable bowel syndrome during remission of ulcerative colitis requires avoidance of a high-fibre diet and possibly treatment with an antispasmodic.

Hydrocortisone

Retention enema.
Suppository: 25 mg (acetate).

Hydrocortisone retention enema is a representative rectal corticosteroid preparation (excluding suppositories). Various formulations can serve as alternatives.

Hydrocortisone rectal preparations are complementary list medicines.

Uses: ulcerative colitis, proctitis, proctosigmoiditis; anaphylaxis (section 3); inflammatory skin conditions (section 13.3); adrenocortical insufficiency (section 18.1).

Contraindications: bowel obstruction, bowel perforation, or extensive fistulas (enemas); untreated infections.

Precautions: proctological examination required before treatment; systemic absorption may occur (see section 18.1); prolonged use should be avoided; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Ulcerative colitis, proctitis, *by rectum* (suppositories), **ADULT,** 25 mg twice daily for 2 weeks; may be increased to 25 mg 3 times daily or 50 mg twice daily in severe cases; in factitial proctitis treatment may be required for 6–8 weeks.

Ulcerative colitis, ulcerative proctitis, ulcerative proctosigmoiditis, *by rectum* (retention enema), **ADULT,** 100 mg at night for 21 days or until clinical and proctological remission; if there is no clinical and proctological improvement after 21 days, discontinue; treatment for 2–3 months may be required for proctological remission; when used for more than 21 days, discontinue gradually using 100 mg every other night for 2–3 weeks.

Adverse effects: local pain or burning sensation; rectal bleeding reported (with use of enema); exacerbation of untreated infections; suppositories may stain fabrics; for adverse effects associated with long-term corticosteroid treatment, see section 18.1.

Sulfasalazine

Retention enema.
Suppository: 500 mg.
Tablet: 500 mg.

Sulfasalazine is a representative aminosalicylate. Various medicines can serve as alternatives.

Uses: ulcerative colitis; Crohn disease; severe rheumatoid arthritis (section 2.4).

Contraindications: hypersensitivity to salicylates or sulfonamides; child under 2 years; porphyria; intestinal or urinary obstruction; severe renal impairment.

Precautions: renal impairment (Appendix 4); hepatic impairment (Appendix 5); G6PD deficiency; slow acetylator status; monitor blood counts and liver function initially and at monthly intervals for first 3 months of treatment; monitor kidney function initially and at intervals during treatment; history of allergy; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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 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.

Ulcerative colitis, Crohn colitis, *by rectum* (suppositories, used alone or in conjunction with oral therapy), **ADULT,** 0.5–1 g morning and evening after a

bowel movement; *by rectum* (retention enema), **ADULT,** 3 g at night retained for at least an hour; **CHILD,** not a suitable formulation.

Adverse effects: nausea, headache, exacerbation of colitis; diarrhoea, loss of appetite, fever, blood disorders (including Heinz body anaemia, megaloblastic anaemia, leukopenia, neutropenia, and thrombocytopenia); hypersensitivity reactions (including rash, urticaria, Stevens-Johnson syndrome (erythema multiforme), exfoliative dermatitis, epidermal necrolysis, pruritus, photosensitization, anaphylaxis, serum sickness, interstitial nephritis, and lupus erythematosus-like syndrome); lung complications (including eosinophilia and fibrosing alveolitis); ocular complications (including periorbital oedema); stomatitis, parotitis; ataxia, aseptic meningitis, vertigo, tinnitus, alopecia, peripheral neuropathy, insomnia, depression, hallucinations; renal effects (including proteinuria, crystalluria, and haematuria); oligospermia; rarely acute pancreatitis, hepatitis; urine may be coloured orange; some soft contact lenses may be stained.

17.4 Laxatives

A balanced diet, including adequate fluid intake and fibre, 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 hypokalaemia.

Laxatives should generally be avoided except where straining will exacerbate a condition such as angina or increase the risk of rectal bleeding, as in haemorrhoids. Laxatives are of value in drug-induced constipation, for the expulsion of parasites after anthelminthic 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 faecal mass and stimulating peristalsis, stimulant laxatives (such as **senna**) which increase intestinal motility and often cause abdominal cramp, faecal softeners which lubricate and soften impacted

faeces 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.

Senna

Tablet: 7.5 mg (sennosides)(or traditional dosage forms)

Senna is a representative stimulant laxative. Various medicines can serve as alternatives.

Uses: constipation (acts in 8–12 hours).

Contraindications: intestinal obstruction; undiagnosed abdominal symptoms

Precautions: avoid prolonged use unless indication for prevention of faecal impaction; breastfeeding (Appendix 3).

Dose:

Constipation, *by mouth*, **ADULT,** 2–4 tablets, usually at night; initial dose should be low, then gradually increased; **CHILD** over 6 years, half the adult dose in the morning (on doctor's advice).

Adverse effects: abdominal discomfort; hypokalaemia (with prolonged use or overdosage).

17.5 Medicines used in diarrhoea

Acute diarrhoeal diseases are a leading cause of childhood morbidity and mortality; frail and elderly patients are also at risk. In adults acute diarrhoea is the most frequent health problem of travellers 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 diarrhoea. Symptomatic relief (section 17.5.3) in adults may be warranted in some cases but antidiarrhoeals should never be used in children since they do not reduce fluid and electrolyte loss and may cause adverse effects.

Diarrhoea persisting for longer than a month is known as chronic diarrhoea. A mild malabsorption syndrome, tropical enteropathy, is apparent in most healthy indigenous populations of tropical countries. However the majority of cases of chronic diarrhoea have non-infectious causes including gluten-sensitivity, inherited metabolic disorders or inflammatory bowel disease. Bloody diarrhoea 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 diarrhoea 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 diarrhoea, 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 and 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 breastfeeding should be increased. Parents should be informed about the circumstances in which they should seek further advice.

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 breastfeeding 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 diarrhoea.

Plan C: severe dehydration. Hospitalization is necessary, but the most urgent priority is to start rehydration. In 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) (section 26.2) 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

Glucose: 75 mEq sodium: 75 mEq or mmol/l chloride: 65 mEq or mmol/l potassium: 20 mEq or mmol/l citrate: 10 mmol/l osmolarity: 245 mOsm/l 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/litre of clean water
sodium citrate [dihydrate]	2.9 g/litre of clean water
potassium chloride	1.5 g/litre of clean water
glucose (anhydrous)	13.5 g/litre of clean water

When glucose and sodium citrate are not available, they may be replaced by

sucrose (common sugar)	27 g/litre of clean water
sodium bicarbonate	2.5 g/litre 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 is important. Administration of more concentrated solutions can result in hypernatraemia.

Uses: dehydration from acute diarrhoea.

Precautions: renal impairment (Appendix 4).

Dose:

Fluid and electrolyte loss in acute diarrhoea, *by mouth*, **ADULT,** 200–400 ml solution after every loose motion; **INFANT** and **CHILD,** according to Plans A, B, or C (see introductory notes above).

Adverse effects: vomiting (may indicate too rapid administration); hypernatraemia and hyperkalaemia (may result from overdose in renal impairment or administration of too concentrated a solution).

17.5.2 Medicines for diarrhoea in children

Zinc sulfate

Oral liquid: in 10 mg per unit dosage forms.
Tablet: in 10 mg per unit dosage forms.

Zinc supplementation is used in combination with oral rehydration therapy in the management of acute diarrhoea in children. Zinc supplements given during an episode of acute diarrhoea reduce the severity and duration of the episode; if given for 10 to 14 days zinc also reduces the incidence of new episodes of diarrhoea in the 2 to 3 months following treatment.

Uses: adjunct to oral rehydration therapy in acute diarrhoea.

Precautions: acute renal failure (may accumulate); **interactions:** Appendix 1.

Dose:

Adjunct to oral rehydration therapy in acute diarrhoea, *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 breastmilk, 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, diarrhoea, gastric irritation, gastritis; irritability, headache, lethargy.

17.5.3 Antidiarrhoeal (symptomatic) medicines in adults

Opioids such as **codeine** are used in the symptomatic relief of uncomplicated, acute diarrhoea 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 (sections 17.5.1 and 26).

Codeine

Tablet: 30 mg (phosphate).

Drug subject to international control under the Single Convention on Narcotic Drugs (1961).

Uses: short-term symptomatic relief of acute diarrhoea in adults; mild to moderate pain (section 2.2).

Contraindications: children; conditions where inhibition of peristalsis should be avoided; abdominal distension; acute diarrhoeal conditions such as ulcerative colitis or antibiotic-associated colitis; acute respiratory depression including asthma attacks.

Precautions: tolerance or dependence may occur with prolonged use; the elderly and debilitated patients; hepatic impairment (Appendix 5); renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); overdosage: see section 4.2; **interactions:** Appendix 1.

Dose:

Symptomatic relief of acute diarrhoea, *by mouth*, **ADULT,** 30 mg 3–4 times daily.

Adverse effects: nausea, vomiting, constipation, drowsiness; respiratory depression and hypotension (with large doses); dependence; difficulty with micturition; ureteric or biliary spasm; dry mouth, sweating, headache, facial flushing, vertigo, bradycardia, tachycardia, palpitations, hypothermia, hallucinations, dysphoria, mood changes, miosis, decreased libido or potency, rash, urticaria, pruritus; convulsions (with large doses).

SECTION 18:
Hormones, other endocrine medicines and contraceptives

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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 [not included on the 15th WHO Model List] also has glucocorticoid properties, it is used for its potent mineralocorticoid effects.

In physiological (low) doses, corticosteroids replace deficient endogenous hormones. In pharmacological (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 effects. 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.

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 (see also note on Withdrawal of systemic corticosteroids below).

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 ceasation of therapy. Abrupt withdrawal after a prolonged period may therefore result in acute adrenal insufficiency, hypotension or even death (see note on 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 re-introduction of corticosteroid treatment. It is important therefore that anaesthetists know whether a patient is taking or has been taking a corticosteroid so as to avoid a precipitous fall in blood pressure during anaesthesia 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 anaesthesia:* 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 anaesthesia, 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, septicaemia and tuberculosis, may reach an advanced stage before being recognized; amoebiasis 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.

Chickenpox

Unless they have already had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at risk of severe chickenpox. Manifestations of fulminant illness include pneumonia, hepatitis, and disseminated intravascular coagulation; rash is not necessarily a prominent feature.

Passive immunization with varicella–zoster immunoglobulin [not included on the 15th WHO Model List] 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 chickenpox 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 chickenpox.

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 oedema 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), eye drops (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 is dependent 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.

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 and 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 is required to prevent masculinizing effects.

Testosterone

Injection: 200 mg (enantate) in 1-ml ampoule.

Testosterone is a complementary list androgenic medicine.

Uses: hypogonadism; palliative treatment of advanced breast cancer in women.

Contraindications: breast cancer in men, prostate cancer; hypercalcaemia; pregnancy (Appendix 2); breastfeeding (Appendix 3); nephrotic syndrome; history of primary liver tumours.

Precautions: cardiac disease; renal impairment (Appendix 4); hepatic impairment (Appendix 5); the elderly; ischaemic heart disease, hypertension; epilepsy, migraine, diabetes mellitus, skeletal metastases (risk of hypercalcaemia); examine prostate and breast regularly during treatment; prepubertal boys; **interactions:** Appendix 1.

Dose:

Hypogonadism, *by slow intramuscular injection*, **ADULT** (males), initially 200–250 mg every 2–3 weeks; usual maintenance dose, 200–250 mg every 3–6 weeks.

Breast cancer, *by slow intramuscular injection*, **ADULT** (females), 250 mg every 2–3 weeks.

Adverse effects: prostate abnormalities and prostate cancer, headache, depression, gastrointestinal bleeding, nausea, polycythaemia, cholestatic jaundice, changes in libido, gynaecomastia, anxiety, asthenia, paraesthesia; electrolyte disturbances including sodium retention with oedema and hypercalcaemia, hypertension, and weight gain; increased bone growth; androgenic effects including hirsutism, male-pattern baldness, seborrhoea, acne, pruritus, priapism, precocious sexual development and premature closure of epiphyses in prepubertal males, virilism in females, and suppression of spermatogenesis in men; rarely liver tumours; sleep apnoea also reported.

18.3 Contraceptives

WHO publishes guidelines on the use of contraceptives, including the *Medical eligibility criteria for contraceptive use*, available at www.who.int/reproductive-health/publications/mec, and the *Selected practice recommendations for contraceptive use*, available at www.who.int/reproductive-health/publications/spr.

Parenteral hormonal contraception

Medroxyprogesterone acetate and norethisterone enantate are long-acting progestogens given by intramuscular injection every 3 months and every 2 months respectively. Women should be counselled about the likelihood of menstrual disturbance and the potential for a delay in return to full fertility; delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility. Heavy bleeding has been reported in patients given parenteral progestogen-only contraceptives in the immediate puerperium (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 (she should be warned that the risk of heavy or prolonged bleeding may be increased). Parenteral progestogen-only contraceptives reliably inhibit ovulation, and 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.

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 amenorrhoea 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, reduce risk of iron-deficiency anaemia, and significant decrease in dysmenorrhoea. 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 [not included on the 15th WHO Model List], 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 which 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 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).

Progestogen-only contraceptives

Progestogen-only contraceptives, such as oral **levonorgestrel,** may offer a suitable alternative when estrogens are contraindicated. However, oral progestogen-only preparations do not prevent ovulation in all cycles and have a higher failure rate than combined estrogen-containing preparations. Progestogen-only contraceptives carry less risk of thromboembolic and cardiovascular disease than combined oral contraceptives and are preferable for women at increased risk of such complications, for example, smokers over 35 years. They can be used as an alternative to estrogen-containing combined preparations prior to major surgery. Oral progestogen-only contraceptives may be started 3 weeks after birth; breastfeeding women should preferably delay starting until at least 6 weeks after birth. Menstrual irregularities (oligomenorrhoea, menorrhagia, amenorrhoea) are common.

Emergency contraception

Levonorgestrel is used for emergency contraception. Levonorgestrel, 1.5 mg, should be taken as a single dose within 120 hours of unprotected intercourse; alternatively, levonorgestrel, 750 micrograms, can be taken within 72 hours of

unprotected intercourse followed 12 hours later by another dose of 750 micrograms. Adverse effects include nausea, vomiting, headache, dizziness, breast discomfort, and menstrual irregularities. If vomiting occurs within 2–3 hours of taking the tablets, replacement tablets can be given with an antiemetic.

It should be explained to the woman that her next period may be early or late; that she needs to use a barrier contraceptive method until her next period, and that she should seek medical advice promptly if she has any lower abdominal pain (because this could signify an ectopic pregnancy) or if the subsequent menstrual bleed is abnormally light, heavy, brief, or absent. There is no evidence of harmful effects to the fetus if pregnancy should occur.

Ethinylestradiol + levonorgestrel

Tablet: 30 micrograms + 150 micrograms.

Ethinylestradiol with levonorgestrelis a representative combined oral contraceptive preparation. Various combinations can serve as alternatives.

Uses: contraception; menstrual symptoms; endometriosis (see also section 18.7).

Contraindications: use within 3 weeks of birth; breastfeeding (until weaning or for the first 6 months after birth; Appendix 3); 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 duration despite treatment or migraine treated with ergot derivatives (see also note below); history of sub-acute bacterial endocarditis; ischaemic cerebrovascular disease; liver disease including disorders of hepatic secretion such as Dubin-Johnson and Rotor syndromes, infectious hepatitis (unless liver function is restored to normal); porphyria; systemic lupus erythematosus; liver adenoma; history of haemolytic uraemic syndrome; gallstones; estrogen-dependent neoplasms; neoplasms of breast or genital tract; undiagnosed vaginal bleeding; history during pregnancy of pruritus, chorea, deteriorating otosclerosis, cholestatic jaundice, or pemphigoid gestationis; after evacuation of hydatidiform mole (unless urine and plasma gonadotrophin values are restored to normal).

Precautions: risk factors for venous thromboembolism and arterial disease (see also note above); migraine without focal aura or controlled with $5HT_1$ agonist (see also note below); hyperprolactinaemia (seek specialist advice); some types of hyperlipidaemia; 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 disease; **interactions:** Appendix 1.

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); *by mouth*, [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.

DIARRHOEA AND VOMITING. Vomiting within 2 hours of taking an oral contraceptive or very severe diarrhoea can interfere with the absorption of the pill. Additional precautions should be used during, and for 7 days after, recovery (see also note on Missed pill above). If vomiting and diarrhoea occur during the last 7 pills, the next pill-free period should be omitted (or in the case of ED tablets, the inactive ones should be omitted).

Adverse effects: nausea, vomiting, headache, breast tenderness, increase in body weight, thrombosis, changes in libido, depression, chorea, skin reactions, chloasma, hypertension, impairment of liver function, "spotting" in early cycles, absence of withdrawal bleeding, irritation of contact lenses; rarely photosensitivity reactions and hepatic tumours; 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

Tablet: 35 micrograms + 1 mg.

Ethinylestradiol with norethisterone is a representative combined oral contraceptive preparation. Various combinations can serve as alternatives.

Uses: contraception; menstrual symptoms; endometriosis (see also section 18.7).

Contraindications: use within 3 weeks of birth; breastfeeding (until weaning or for the first 6 months after birth; Appendix 3); 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 duration despite treatment or migraine treated with ergot derivatives (see also note below); history of sub-acute bacterial endocarditis; ischaemic cerebrovascular disease; liver disease including disorders of hepatic secretion such as Dubin-Johnson and Rotor syndromes, infectious hepatitis (unless liver function is restored to normal); porphyria; systemic lupus erythematosus; liver adenoma; history of haemolytic uraemic syndrome; gallstones; estrogen-dependent neoplasms; neoplasms of breast or genital tract; undiagnosed vaginal bleeding; history during pregnancy of pruritus, chorea, deteriorating otosclerosis, cholestatic jaundice, or pemphigoid gestationis; after evacuation of hydatidiform mole (unless urine and plasma gonadotrophin values are restored to normal).

Precautions: risk factors for venous thromboembolism and arterial disease (see also note above); migraine without focal aura or controlled with $5HT_1$ agonist (see also note below); hyperprolactinaemia (seek specialist advice); some types of hyperlipidaemia; 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 disease; **interactions:** Appendix 1.

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); *by mouth*, [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.

DIARRHOEA AND VOMITING. Vomiting within 2 hours of taking an oral contraceptive or very severe diarrhoea can interfere with the absorption of the pill. Additional precautions should be used during, and for 7 days after, recovery (see also note on Missed pill above). If vomiting and diarrhoea occur during the last 7 pills, the next pill-free period should be omitted (or in the case of ED tablets, the inactive ones should be omitted).

Adverse effects: nausea, vomiting, headache, breast tenderness, increase in body weight, thrombosis, changes in libido, depression, chorea, skin reactions, chloasma, hypertension, impairment of liver function, "spotting" in early cycles, absence of withdrawal bleeding, irritation of contact lenses; rarely photosensitivity reactions and hepatic tumours; 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).

Levonorgestrel

Tablet: 30 micrograms; 750 micrograms (pack of two); 1.5 mg.

Uses: contraception (particularly when estrogens are contraindicated); emergency hormonal contraception.

Contraindications: contraception: severe arterial disease; liver tumours; 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; breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Contraception, *by mouth*, **ADULT** (female), 1 tablet (30 micrograms) 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.

DIARRHOEA AND VOMITING. Vomiting within 2 hours of taking an oral contraceptive or very severe diarrhoea can interfere with the absorption of the pill. Additional precautions should be used during and for 2 days after recovery (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

ADMINISTRATION. Taking emergency contraception as soon as possible after unprotected intercourse increases its efficacy; however, it should not be administered if menstrual bleeding is already overdue.

Adverse effects: menstrual irregularities (including oligomenorrhoea 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).

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 counselled 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 breastfeeding, 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, and 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 stablizes.

Medroxyprogesterone acetate + estradiol cipionate is a combined progestogen plus estrogen preparation given monthly by intramuscular injection. Medroxyprogesterone + estradiol cipionate is associated with fewer menstrual disturbances and a faster return to fertility after discontinuation than progestogen-only contraceptives.

Estradiol cypionate + medroxyprogesterone acetate

Injection: 5 mg + 25 mg.

Uses: parenteral combined progestogen-estrogen contraception (short-term).

Contraindications: see under Combined oral contraceptives (section 18.3.1).

Precautions: see under Combined oral contraceptives (section 18.3.1); **interactions:** Appendix 1 (see under Contraceptives, oral).

Dose:

Contraception, *by deep intramuscular injection*, **ADULT** (female), estradiol cipionate, 5 mg + medroxyprogesterone acetate, 25 mg, as a single dose within the first 7 days of the menstrual cycle, repeated monthly.

ADMINISTRATION. If the interval between injections is greater than 35 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.

Adverse effects: menstrual irregularities (usually stabilize after initial months of use); less commonly weight gain, headache, and dizziness; abdominal pain, acne, alopecia, asthenia, breast tenderness, decreased libido, depression, enlarged abdomen, nausea, nervousness, and vulvovaginal disorder reported.

Medroxyprogesterone acetate

Depot injection: 150 mg/ml in 1-ml vial.

Uses: parenteral progestogen-only contraception (short- or long-term); menstrual symptoms and endometriosis (section 18.7).

Contraindications: pregnancy (Appendix 2); 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 5); severe arterial disease; multiple risk factors for venous thromboembolism and arterial disease (see note in section 18.3.1); porphyria.

Precautions: migraine; liver disease (Appendix 5); thromboembolic or coronary vascular disease; diabetes mellitus; hypertension; renal disease; **interactions:** Appendix 1.

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 breastfeeding).

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 counselling (backed by a manufacturer's approved leaflet if possible) about the likelihood of menstrual irregularities and the potential for a delay in return to full fertility with long-term use.

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).

Norethisterone enantate

Oily injection: 200 mg/ml in 1-ml ampoule.

Uses: parenteral progestogen-only contraception (short-term).

Contraindications: see under Medroxyprogesterone acetate.

Precautions: see under Medroxyprogesterone acetate; **interactions:** Appendix 1.

Dose:

Short-term contraception, *by deep intramuscular injection* into gluteal muscle, **ADULT** (female), 200 mg within the first 7 days of the menstrual cycle or immediately after parturition; repeated after 2 months.

ADMINISTRATION. If the interval between injections is greater than 2 months and 14 days, exclude pregnancy before administering the next injection and advise patient to use additional contraceptive measures (for example, a condom) for 7 days after the injection.

PATIENT ADVICE. It is recommended that before treatment, women receive full counselling (backed by a manufacturer's approved leaflet if possible) about the likelihood of menstrual irregularities and the potential of delay in the return to full fertility with long-term use.

Adverse effects: bloating, breast discomfort, headache, dizziness, depression, nausea, menstrual irregularities; delayed return to fertility; rarely weight gain; injection-site reactions.

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, copper intrauterine device fitted in a woman over 40 years of age, may remain in the uterus until the menopause.

The intrauterine device (or "coil") is appropriate for women who expect to use it for continuous long-term contraception. It is suitable for older parous women; intrauterine devices 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 counselling 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 pre-existing lower genital tract infections. Pre-screening (at least for chlamydia and gonorrhoea) should be performed if feasible and appropriate. If sustained pelvic or lower abdominal pain occur during the following 20 days after insertion of the device, the woman should be treated as having acute pelvic inflammatory disease.

An intrauterine device 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, haemorrhage, pre-term 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 anaemia; use within 48 hours–4 weeks of birth; puerperal sepsis; postseptic 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 disease; medical diathermy.

Precautions: anaemia; heavy menstrual bleeding, endometriosis, severe primary dysmenorrhoea, history of pelvic inflammatory disease, ovarian cancer, fertility problems, nulliparity and young age, severely scarred uterus or severe cervical stenosis, valvular heart disease or history of endocarditis (antibacterial cover recommended at insertion); HIV infection or immunosuppressive therapy (increased risk of infection; avoid if marked immunosuppression); increased risk of expulsion if inserted before uterine involution; gynaecological examination before insertion and 4–6 weeks afterwards (counsel women to see doctor promptly if significant symptoms, such as pain, occur; anticoagulant therapy; remove if pregnancy occurs (consider possibility of ectopic pregnancy).

Administration:

Contraception, **ADULT** (female), *insert* 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 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; dysmenorrhoea; 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 condoms, male non-latex condoms or female non-latex condoms; diaphragm or cervical caps.

Uses: contraception; for condoms, also to decrease risk of transmission of HIV and other sexually transmitted diseases.

Precautions: oil-based products including baby oil, massage oil, lipstick, petroleum jelly, sun-tan oil (can damage latex condoms and render them

less effective as barrier method of contraception and as a protection from sexually transmitted infections, including HIV — if a lubricant is required, use one that is water-based); 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 or diaphragm not suitable for women at high risk of HIV infection or with HIV infection.

Adverse effects: vaginal and cervical irritation (spermicides), toxic shock syndrome (diaphragm, cap).

18.3.5 Implantable contraceptives

Levonorgestrel is a progestogen, which is available as a subdermal implant. It provides long-term contraception, which is rapidly reversed upon removal. **Levonorgestrel implants** are an alternative for women in whom copper-containing intrauterine devices (section 18.3.3) are unsuitable because of pelvic inflammatory disease, dysmenorrhoea, or heavy menstrual bleeding. Levonorgestrel implant insertion and removal requires training.

Levonorgestrel-releasing implant

Two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg total).

Uses: parenteral progestogen-only contraception (long-term).

Contraindications: pregnancy (Appendix 2); ischaemic heart disease, stroke; migraine with aura; thromboembolic disorders, unexplained vaginal bleeding; breast cancer; active viral hepatitis, severe liver disease (Appendix 5); liver tumours.

Precautions: hypertension, heart disease, history of thromboembolism, epilepsy, migraine without aura, depression, gallbladder disease, diabetes mellitus, elevated cholesterol or triglycerides; breast nodules; breastfeeding (until weaning or for the first and less 6 months after birth; Appendix 3); **interactions:** Appendix 1.

Administration:

Contraception (long-term), **ADULT** (female), 150 mg implant; *insert subdermally* in non-dominant upper arm 6–8 cm above the elbow within the first 7 days of the menstrual cycle; remove and replace after 4–5 years depending on preparation.

NOTE. Implant insertion and removal requires specialist training (consult manufacturer's literature).

Adverse effects: menstrual irregularities, headache, dizziness, lower abdominal pain, weight gain, acne; nausea, mood changes, breast tenderness, and loss of libido also reported.

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 the menopause.

Estrogen therapy is given cyclically or continuously principally for contraception(sections 18.3.1 and 18.3.2) 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.

Hormone replacement therapy

Estrogens are used for replacement therapy in perimenopausal and menopausal women who are unduly affected by symptoms such as vasomotor instability and vulval and vaginal atrophy. Estrogens can also help to prevent postmenopausal osteoporosis but drugs that have a specific effect on bone metabolism are now preferred for this condition.

Hormone replacement therapy (HRT) does not prevent coronary heart disease, nor does it protect against a decline in cognitive function and it should **not** be prescribed for these reasons. The minimum effective dose of HRT should be used for the shortest duration possible, and treatment should be reviewed at least annually.

While a short course of a topical vaginal estrogen preparation can relieve symptoms of vulval and vaginal atrophy, systemic HRT is required to alleviate vasomotor symptoms.

In women with an intact uterus (or endometrial foci), the addition of a progestogen to the estrogen therapy reduces the risk of endometrial cancer (but can slightly increase the risk of breast cancer). Medroxyprogesterone

acetate may be given in a dose of 10 mg daily for the last 12–14 days of each cycle of estrogen therapy. Alternatively, norethisterone, 1 mg daily, may be given on the last 12–14 days of each 28-day estrogen cycle (see also section 18.7).

HRT may be considered for women with early natural or surgical menopause (before the age of 45 years); however, alternatives to HRT should be considered if osteoporosis is the main concern. For early menopause, HRT can be given until the approximate age of natural menopause (until the age of 50 years).

Risks of HRT

When prescribing HRT, women must be made 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; women of African origin appear to be less susceptible to osteoporosis than those who are white or of Asian origin.

There is an increased risk of *deep-vein thrombosis* and of *pulmonary embolism* in women taking HRT, especially in the first year of use. About 10 in every 1000 women aged 50–59 years not using HRT develop venous thromboembolism over 5 years; this figure rises by about 1 extra case in 1000 in those using estrogen-only HRT for 5 years and about 4 extra cases in 1000 in those using combined HRT (an estrogen and a progestogen) for 5 years. About 20 in every 1000 women aged 60–69 years not using HRT develop venous thromboembolism over 5 years; this figure rises by about 4 extra cases in 1000 in those using estrogen-only HRT for 5 years and about 9 extra cases in 1000 in those using combined HRT for 5 years. In women who have predisposing factors, such as a personal or family history of deep-vein thrombosis or pulmonary embolism, severe varicose veins, obesity, surgery, trauma, or prolonged bedrest, the overall risk associated with HRT may outweigh the benefit. Travel involving prolonged immobility also increases the risk of venous thromboembolism.

Using HRT increases the risk of *breast cancer* slightly. The increased risk is related to the duration of HRT use and this excess risk disappears within about 5 years of stopping. The risk of breast cancer is greater with combined HRT than with estrogen-only HRT (but as indicated above, estrogen alone may not be suitable for women with an intact uterus).

In women aged between 50 and 64 years not using HRT, a breast cancer will be diagnosed in about 14 out of every 1000 women over 5 years. In women using combined HRT for 5 years, there will be about 6 additional cases in 1000; in women using estrogen-only HRT for 5 years, there will be about 1.5 additional cases in 1000.

In women aged between 50 and 79 years not using HRT, breast cancer will be diagnosed in about 31 out of every 1000 women over 5 years. In women using combined HRT for 5 years, there will be about 4 additional cases in 1000; in women using estrogen-only HRT for 5 years, there will be no additional cases of breast cancer diagnosed.

HRT slightly increases the risk of *stroke*. About 3 in every 1000 women aged 50–59 years not using HRT have a stroke over 5 years; this figure rises by about 2 additional cases in 1000 in those using estrogen-only HRT for 5 years and by about 1 additional case in those using combined HRT for 5 years. About 26 in every 1000 women aged 60–69 years not using HRT have a stroke over 5 years; this figure rises by about 6 additional cases in 1000 in those using an estrogen-only HRT for 5 years and by about 4 additional cases in those using combined HRT for 5 years.

HRT possibly increases the risk of coronary heart disease in the first year of use.

About 3 in every 1000 women aged 50–69 not using HRT will have *endometrial cancer* diagnosed over 5 years; in those using estrogen-only HRT for 5 years, there will be about 5 additional cases in 1000. The excess risk of endometrial cancer cannot be reliably estimated in those using combined HRT because the addition of a progestogen for at least 12 days per month greatly reduces the additional risk.

About 3 in every 1000 women aged 50–69 years not using HRT have *ovarian cancer* diagnosed over 5 years; this figure rises by about 1 additional case in 1000 in those using estrogen-only HRT for 5 years; the excess risk in women using combined HRT is unknown.

HRT does not provide contraception. If a potentially fertile woman needs to use HRT, non-hormonal contraceptive measures are necessary.

Precautions for patients on HRT undergoing surgery and reasons for stopping HRT are the same as those for oral hormonal contraceptives (see notes on surgery and Reasons to stop combined oral contraceptives immediately in section 18.3.1).

Ethinylestradiol

Tablet: 10 micrograms; 50 micrograms.

Ethinylestradiol is a representative estrogen. Various medicines can serve as alternatives.

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 2); estrogen-dependent cancer; active thrombophlebitis or thromboembolic disorders or history of recent venous thromboembolism (unless already on anticoagulant therapy); undiagnosed vaginal bleeding; breastfeeding (Appendix 3); 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 of 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 tumours; porphyria; **interactions:** Appendix 1.

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,** 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 hyperglycaemia 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 to reduced secretion of insulin from the pancreas or to peripheral resistance to the action of insulin. Type 2 diabetes may be controlled by diet alone, but often those with this form of the disease require administration of oral antidiabetic drugs or insulin. The energy and carbohydrate intake must be adequate but obesity should be avoided. In type 2 diabetes, obesity is one of the factors associated with insulin resistance. Diets high in complex carbohydrate and fibre and low in fat are beneficial. Emphasis should be placed on exercise and increased activity.

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 hyperlipidaemia, should also be addressed.

Insulin

Appropriate insulin regimens should be worked out for each patient. Insulin requirements may be affected by variations in lifestyle (diet and exercise). Concomitant use of drugs such as corticosteroids, presence of infections, stress, accidental or surgical trauma, puberty and pregnancy (second and third trimesters) tend to increase insulin requirements; renal or hepatic impairment and some endocrine disorders (for example, Addison disease and hypopituitarism) or coeliac disease, usually reduce requirements. In pregnancy, insulin requirements should be monitored frequently.

Insulin must be given by injection because it is inactivated by gastrointestinal enzymes. Generally, insulin is given by subcutaneous injection into the upper arms, thighs, buttocks, or abdomen. There may be increased absorption from a limb site, if the limb is used in strenuous exercise following the injection. It is essential to use only syringes calibrated for the particular concentration of insulin administered.

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.

Soluble insulin, when injected subcutaneously, has a rapid onset of action (after 30–60 minutes), a peak action between 2 and 4 hours, and a duration of action of up to 8 hours. Soluble insulin by the intravenous route is reserved for urgent treatment and fine control in serious illness and perioperatively. When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes and its effect disappears within 30 minutes.

When injected subcutaneously, **intermediate-acting insulins** take effect within approximately 1–2 hours, within a maximal effect at 4–12 hours and a duration of action of 16–24 hours. They can be given twice daily (together with short-acting insulin) or once daily, particularly in elderly patients. Most can be mixed with soluble insulin in the syringe, administered together while retaining the properties of each component.

Long-acting insulins [not included on the 15th WHO Model List] have an onset of action approximately 4 hours after subcutaneous injection; peak activity is between 10 and 20 hours, and duration of action is up to 36 hours. Mixed insulin zinc suspension can be classified as either intermediate or long-acting.

The duration of action of different insulin preparations varies considerably from one patient to another and this needs to be assessed for every individual. The type of insulin used, and also its dose and frequency of administration, depend on the precise requirements of each patient. For patients with acute onset diabetes mellitus, treatment should be started with soluble insulin given 3 times daily with medium-acting insulin at bedtime. For those less seriously ill, treatment is usually started with a mixture of pre-mixed short- and medium-acting insulins (for example, 30% soluble insulin and 70% isophane insulin) given twice daily. The proportions of soluble insulin can be increased in patients with excessive post-prandial hyperglycaemia.

Regimens should be developed by each country.

Monitoring

If possible, patients should monitor their own blood glucose concentration using blood glucose strips. Blood glucose concentration varies throughout the day; diabetics should aim to maintain their blood glucose concentration between 4 and 9 mmol/litre for most of the time (ideally, 4–7 mmol/litre before meals and less than 9 mmol/litre after meals) while accepting that on occasions it will be higher; strenuous efforts should be made to prevent blood-glucose concentration falling below 4 mmol/litre because of the risk of hypoglycaemia. Patients should be advised on how to look for troughs and peaks in their own blood glucose and to adjust their insulin dosage accordingly,

but preferably only once or twice a week. Insulin doses are determined on an individual basis, by gradually increasing the dose to optimize blood glucose concentration while avoiding hypoglycaemia.

In the absence of blood glucose monitoring strips, urine glucose monitoring strips can be used; in fact this is the method of personal choice for many patients with Type 2 diabetes mellitus. It is less reliable than blood glucose but is easier and costs much less. All patients should monitor either blood or urine glucose concentration daily.

Hypoglycaemia

Hypoglycaemia is a potential complication in all patients treated with insulin or less frequently with sulfonylureas. The consequences of hypoglycaemia include confusion, seizures, coma, and cerebral infarction.

Loss of warning of hypoglycaemia is common among insulin-treated patients and can be a serious hazard, especially for drivers and those in dangerous occupations. It is vital that patients maintain a very tight control on their blood glucose in order to manage their condition; not only does tight control lower the blood glucose concentration needed to trigger hypoglycaemic symptoms; but any increase in the frequency of hypoglycaemic episodes reduces the warning symptoms experienced by patients. Beta-blockers can also blunt hypoglycaemic awareness (and delay recovery). Some patients report loss of hypoglycaemic warning after transfer to human insulin. Although clinical studies do not confirm that human insulin decreases hypoglycaemic awareness, if a patient believes that human insulin is responsible for loss of warning, it is reasonable to revert to animal insulin. To restore warning signs, episodes of hypoglycaemia must be reduced to a minimum; this involves appropriate adjustment of insulin dose and frequency, and careful attention to the timing and quantity of meals and snacks.

For sporadic physical activity, extra carbohydrate may need to be taken to avert hypoglycaemia. Blood glucose should be monitored before, during, and after exercise.

Initial treatment of "mild to moderate" hypoglycaemia involves glucose, 10–20 g, given by mouth either in liquid form or as granulated sugar (2 teaspoons) or sugar lumps (3 lumps). If necessary, this may be repeated after 10–15 minutes.

Hypoglycaemia which causes unconsciousness is medical emergency. Glucagon [not included on the 15th WHO Model List], a polypeptide hormone produced by the alpha cells of the islets of Langerhans, increases plasma glucose concentration by mobilizing glycogen stored in the liver. In severe hypoglycaemia, if sugar cannot be given by mouth, glucagon can be given by injection. Carbohydrates should be given as soon as possible to

restore liver glycogen. If injection of glucagon is not effective in 10 minutes, intravenous glucose should be given. Note that glucagon is not appropriate for the treatment of chronic hypoglycaemia.

Alternatively, 50 ml of glucose solution, 20% [not included on the 15th WHO Model List] may be given intravenously into a large vein through a large gauge needle; care is required since at this concentration glucose solution is irritant, especially if extravasation occurs. Alternatively, 25 ml of glucose solution, 50% (section 26.2) may be given, but this higher concentration solution is even more irritant and viscous, which makes administration difficult. Glucose solution, 10% (section 26.2) may also be used but a larger volume is needed. In the case of hypoglycaemia caused by an overdose with a long-acting insulin, close monitoring is necessary because further administration may be required. Patients whose hypoglycaemia is caused by a sulfonylurea should be transferred to hospital because the hypoglycaemic effects of these drugs may persist for many hours.

Driving

Drivers need to be particularly careful to avoid hypoglycaemia. Insulin-dependent diabetics should normally check their blood glucose concentration before driving and, on long journeys, at intervals of approximately two hours; they should ensure that a supply of sugar is always readily available and avoid driving if their meal has been delayed. If hypoglycaemia occurs or warning signs appear, the driver should stop the vehicle in a safe place, ingest a suitable sugar supply and wait until recovery is complete (may be 15 minutes or longer). Driving is particularly hazardous when hypoglycaemic awareness is impaired.

Diabetic ketoacidosis

Diabetic ketoacidosis is a potentially lethal condition caused by an absolute or relative lack of insulin; it commonly occurs when adjustments to insulin dosage fail to compensate for increases in insulin requirements, for example, during severe infection or a major intercurrent illness. Diabetics ketoacidosis occurs mostly in patients with Type 1 diabetes mellitus. It also occurs in Type 2 diabetics who have a temporary need for insulin. Diabetic ketoacidosis is characterized by hyperglycaemia, hyperketonaemia, and acidaemia, leading to dehydration and electrolyte disturbances. It is essential that soluble insulin and intravenous fluids are readily available for the treatment of this condition.

Infections

Infections are more likely to develop in patients with poorly controlled diabetes mellitus. These should be treated promptly and effectively to avoid diabetic ketoacidosis.

Surgery

Particular attention should be paid to insulin requirements when a patient with diabetes undergoes surgery, especially when surgery is likely to need an intravenous infusion of insulin for longer than 12 hours. Soluble insulin should be given in an intravenous infusion of glucose and potassium chloride (provided the patient is not hyperkalaemic), and the amount adjusted to provide a blood glucose concentration of between 7 and 12 mmol/litre. The duration of action of intravenous insulin is only a few minutes, and therefore the infusion must not be stopped unless the patient becomes severely hypoglycaemic. In non-insulin dependent diabetics, insulin treatment is also almost always required during surgery (oral hypoglycaemic drugs having been omitted).

Oral antidiabetic drugs

Oral antidiabetic (hypoglycaemic) 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 hypoglycaemia 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 breastfeeding and caution is required in the elderly and those with renal or hepatic insufficiency because of the risk of hypoglycaemia. 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 only act 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. Gastrointestinal adverse effects are common on initial treatment and may persist, particularly when very high doses (such as 3 g daily) are given. In order to reduce gastrointestinal effects, treatment should be initiated with a low dose, and increased gradually. Metformin may provoke lactic acidosis; this is most likely to occur in patients with renal impairment; and thus metformin should

not be used in patients with even mild renal impairment. One major advantage of metformin is that it does not usually cause hypoglycaemia. It may be used with insulin (although the weight gain and hypoglycaemia can be problems, weight gain can be minimized if insulin is given at night) or sulfonylureas (possibility of increased adverse effects with such combinations remains unconfirmed). During medical and surgical emergencies, insulin treatment is almost always required; insulin should be substituted for metformin before elective surgery and in pregnancy.

Glibenclamide

Tablet: 2.5 mg; 5 mg.

Uses: diabetes mellitus.

Contraindications: ketoacidosis; porphyria; breastfeeding (Appendix 3).

Precautions: pregnancy (Appendix 2); renal impairment (Appendix 4); hepatic impairment (Appendix 5); the elderly (reduce dose); substitute insulin during intercurrent illness severe infection, trauma, surgery, and pregnancy (see also introductory note above); **interactions:** Appendix 1.

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 (maximum, 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; hypoglycaemia, particularly in the elderly; rarely blood disorders including leukopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, and aplastic anaemia.

Insulin injection (soluble)

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 4); pregnancy (Appendix 2); and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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 oedema; hypoglycaemia in overdose; rarely hypersensitivity reactions including urticaria and rash; local reactions and lipoatrophy at injection site.

Intermediate-acting insulin

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 4); pregnancy (Appendix 2); and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Diabetes mellitus, *by subcutaneous injection*, **ADULT** and **CHILD,** according to individual requirements (see also introductory note above).

Adverse effects: hypoglycaemia in overdose; rarely hypersensitivity reactions, including urticaria and rash; local reactions and lipoatrophy at injection site.

Metformin

Tablet: 500 mg (hydrochloride).

Uses: diabetes mellitus.

Contraindications: renal impairment (Appendix 4); 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 anaesthesia (suspend metformin on the morning of surgery and restart when renal function returns to normal); alcohol dependence; pregnancy (Appendix 2).

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); breastfeeding (Appendix 3); **interactions:** Appendix 1.

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, diarrhoea (usually transient), abdominal pain, metallic taste; rarely lactic acidosis (most likely in patients with renal impairment; discontinue); decreased vitamin B_{12} 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 counselled 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

Tablet: 50 mg (citrate).

Clomifene citrate is a complementary list medicine for fertility treatment.

Uses: anovulatory infertility.

Contraindications: hepatic disease (Appendix 5); ovarian cysts; hormone dependent tumours or uterine bleeding of undetermined cause; pregnancy (exclude before treatment; Appendix 2).

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); breastfeeding (Appendix 3).

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 (sections 18.3.1 and 18.3.5), **norethisterone,** and **medroxyprogesterone**.

Where endometriosis requires drug treatment, it may respond to a synthetic progestogen given on a continuous basis. A progestogen may also be used for the treatment of severe dysmenorrhoea but where contraception is also required, the best choice is a combined oral contraceptive (see section 18.3.1). In postmenopausal women receiving long-term estrogen therapy for hormone replacement, a progestogen needs to be added for women with an intact uterus to prevent hyperplasia of the endometrium (section 18.4). Progestogens have been used for the treatment of menorrhagia, but they are not as effective as tranexamic acid [not included on the 15th WHO Model List]; mefenamic acid [not included on the 15th WHO Model List] is particularly useful where dysmenorrhoea is also a problem. Medroxyprogesterone is also used in the treatment of endometrial cancer.

Progestogens are also used in combined oral contraceptives and progestogen-only contraceptives (section 18.3.1).

Medroxyprogesterone acetate

Tablet: 5 mg.

Medroxyprogesterone acetate is a complementary list progestogenic medicine.

Uses: endometriosis; dysfunctional uterine bleeding; secondary amenorrhoea; endometrial cancer; contraception (section 18.3.2); adjunct in hormone replacement therapy (section 18.4).

Contraindications: pregnancy (Appendix 2); hormone-dependent breast or genital neoplasms; undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 5); severe arterial disease; porphyria.

Precautions: small increase in possible risk of breast cancer; migraine; depression; thromboembolic or coronary vascular disease; diabetes mellitus; trophoblastic disease; hypertension; renal disease (Appendix 4); breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Mild to moderate endometriosis, *by mouth*, **ADULT** (female), 10 mg 3 times daily for 90 consecutive days, beginning on day 1 of cycle.

Dysfunctional uterine bleeding, *by mouth*, **ADULT** (female), 2.5–10 mg daily for 5–10 days, beginning on day 16 to 21 of cycle for 2 cycles.

Secondary amenorrhoea, *by mouth*, **ADULT** (female), 2.5–10 mg daily for 5–10 days beginning on day 16 to 21 of cycle for 3 cycles.

Endometrial cancer, *by mouth*, **ADULT** (female), 200–400 mg daily.

Adverse effects: acne, urticaria, fluid retention, weight gain, gastrointestinal disturbances, changes in libido, breast discomfort, premenstrual symptoms, irregular menstrual cycles; depression, insomnia, somnolence, headache, alopecia, hirsutism; anaphylactoid reactions; rarely jaundice; breast cancer (small increased risk of breast cancer).

Norethisterone

Tablet: 5 mg.

Uses: endometriosis; menorrhagia; severe dysmenorrhoea; contraception (section 18.3.2); hormone replacement therapy (section 18.4).

Contraindications: pregnancy (Appendix 2); undiagnosed vaginal bleeding; hepatic impairment or active liver disease (Appendix 5); 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 4) and those susceptible to thromboembolism; depression; breastfeeding (Appendix 3); **interactions:** Appendix 1.

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.

Dysmenorrhoea, *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 (myxoedema) and also in diffuse non-toxic goitre, Hashimoto thyroiditis (lymphadenoid goitre) 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 myxoedema 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 [not included on the 15th WHO Model List] 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 few per cent 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 which is continued for 12–18 months, followed by monitoring to identify relapse. There is a lag time of some 2 weeks between the achievement of biochemical euthyroidism and clinical euthyroidism. Beta-adrenoceptor antagonists (beta-blockers), usually propranolol, may be used as a short-term adjunct to antithyroid drugs to control symptoms but their use in heart failure associated with thyrotoxicosis is controversial.

If necessary, treatment can be given, in pregnancy but antithyroid drugs cross the placenta and in high doses may cause fetal goitre and hypothyroidism. The lowest dose that will control the hyperthyroid state should be used (requirements in Graves disease tend to fall during pregnancy). Propylthiouracil appears in breast milk but its use does not preclude breastfeeding 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.

Levothyroxine

Tablet: 50 micrograms; 100 micrograms (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); the elderly; long-standing hypothyroidism; diabetes insipidus or diabetes mellitus (may need to increase dose of insulin or oral antidiabetic drug); pregnancy (Appendix 2), breastfeeding (Appendix 3); **interactions:** Appendix 1.

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;

usual maintenance dose, 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 myxoedema (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, diarrhoea, vomiting, tremors, restlessness, excitability, insomnia, headache, flushing, sweating, excessive loss of weight and muscular weakness.

Potassium iodide

Tablet: 60 mg.

Uses: thyrotoxicosis (pre-operative treatment); sporotrichosis, subcutaneous phycomycosis (section 6.3).

Contraindications: breastfeeding (Appendix 3); long-term treatment.

Precautions: pregnancy (Appendix 2); children.

Dose:

Pre-operative 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, goitre in infants of mothers taking iodides.

Propylthiouracil

Tablet: 50 mg.

Propylthiouracil is a representative antithyroid drug. Various medicines can serve as alternatives.

Uses: hyperthyroidism.

Precautions: large goitre; pregnancy and breastfeeding (see also introductory note above; Appendix 2); breastfeeding (see also introductory note above; Appendix 3); hepatic impairment (withdraw treatment if hepatic function deteriorates — fatal reactions reported; Appendix 5); renal impairment (reduce dosage; Appendix 4).

Dose:

Hyperthyroidism, *by mouth*, **ADULT,** 300–600 mg daily until patient becomes euthyroid; dose may then be gradually reduced to a maintenance dose of 50–150 mg daily.

PATIENT ADVICE. Warn patient to tell doctor immediately if either sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness occurs.

Adverse effects: nausea, rash, pruritus, arthralgia, headache; rarely alopecia, cutaneous vasculitis, thrombocytopenia, aplastic anaemia, lupus erythematosus-like syndrome, jaundice, hepatitis, hepatic necrosis, encephalopathy, and nephritis.

SECTION 19:
Immunologicals

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Active immunity

Active immunity may be induced by the administration of micro-organisms 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 which 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 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)

Injection.

All tuberculins should comply with the WHO Requirements for Tuberculins (Revised 1985). In: WHO Expert Committee on Biological Standardization Thirty-sixth report. WHO Technical Report Series, No.745, 1987, Annex 1.

Uses: test for hypersensitivity to tuberculoprotein.

Contraindications: should not be used within 4 weeks of receiving a live viral vaccine.

Precautions: the 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, or mouth.

Dose:

NOTE. National recommendations may vary.

Test for hypersensitivity to tuberculoprotein, *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 (see section 19.3) which should normally 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)

Injection: 250 micrograms in single-dose vial.

Anti-D immunoglobulin is prepared from plasma with a high titre 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 haemolytic disease of the newborn. It should be administered following any potentially sensitizing episode (for example, abortion, miscarriage, or still-birth), ideally immediately or within 72 hours of the episode but even if a longer period has elapsed, it may still give protection and should be used. The dose of 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.

Uses: prevention of formation of antibodies to rhesus-positive blood cells in rhesus-negative patients.

Contraindications: see introductory notes; also 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 1.

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:

NOTE. National recommendations may vary.

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, still-birth), *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 Rh_0 (D) incompatible blood transfusion, *by intramuscular injection*, **ADULT,** 10–20 micrograms per ml transfused rhesus-positive blood.

Adverse effects: see introductory notes.

Antitetanus immunoglobulin (human)

Injection: 500 IU in vial.

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 toilet 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.

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:

NOTE. National recommendations may vary.

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.

Antivenom immunoglobulins

Injection: exact type to be defined locally.

Acute envenoming from snakes or spiders is common in many parts of the world. The bite may cause local and systemic effects.

Local effects include pain, swelling, bruising, and tender enlargement of regional lymph nodes. Wounds should be cleaned and pain may be relieved by analgesics (see section 2.1).

If significant amounts of toxin are absorbed after a snake bite, this may result in early anaphylactoid symptoms such as transient hypotension, angioedema, abdominal colic, diarrhoea, and vomiting, followed by persistent or recurrent hypotension and ECG abnormalities. Spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome, and acute renal failure may also occur. Early anaphylactoid symptoms may be treated with epinephrine (adrenaline). **Snake antivenom immunoglobulins** are the only specific treatment available but they can produce severe adverse reactions. They are generally only used if there is a clear indication of systemic involvement or severe local involvement or, in regions where supplies are not limited, in patients at high risk of systemic or severe local involvement.

Spider bites may cause either necrotic or neurotoxic syndromes depending on the species involved. Supportive and symptomatic treatment is required and in the case of necrotic syndrome, surgical repair may be necessary. **Spider antivenom immunoglobulin,** suitable for the species involved, may prevent symptoms if administered as soon as possible after envenomation.

NOTE. There are many antivenom immunoglobulins, each containing specific venom-neutralizing globulins. It is important that the specific antivenom immunoglobulin suitable for the species causing the envenomation is administered.

Uses: treatment of snake bites and spider bites.

Precautions: resuscitation facilities should be immediately available.

Dose:

Depends on the specific antivenom used; consult manufacturer's literature.

Adverse effects: serum sickness; anaphylaxis with hypotension, dyspnoea, urticaria, and shock.

Diphtheria antitoxin

Injection: 10 000 IU; 20 000 IU in vial.

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.

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:

NOTE. National recommendations may vary.

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, dyspnoea, and shock; serum sickness up to 12 days after injection.

Rabies immunoglobulin

Injection: 150 IU/ml in vial.

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.

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:

NOTE. National recommendations may vary.

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.

19.3 Vaccines

Selection of vaccines from the WHO Model List of Essential Medicines by individual countries should be made after consideration of international recommendations, epidemiology, and national priorities.

National immunization schedules may vary from those presented in this edition of the WHO Model Formulary.

All vaccines should comply with WHO recommendations for the production, control, and evaluation of vaccines and other biological substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers and are available from the WHO web site: www.who.int/biologicals/publications/trs/areas/en/index.html.

WHO publishes regularly-updated advice on vaccines against diseases of international relevance; the advice deals primarily with large-scale immunization programmes. The advice is available from the WHO web site: www.who.int/immunization/documents/positionpapers_intro/en/index.html.

The Strategic Advisory Group of Experts on Immunization (SAGE) regularly reports on a range of issues, including vaccine research and immunization against all vaccine-preventable diseases. The current SAGE reports and recommendations are also available from the WHO web site: www.who.int/immunization/sage_conclusions/en/index.html.

The Global Advisory Committee on Vaccine Safety (GACVS) reports on vaccine safety issues. The current GACVS reports are available via the WHO web site: www.who.int/vaccine_safety/en/.

The WHO web site also has links to further information about the use of vaccines; go to: www.who.int/immunization/en.

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 micro-organism. 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 know 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. Where tuberculosis remains highly prevalent, routine immunization of infants within the first year of life with **BCG vaccine**, derived from bacillus Calmette-Guérin (an attenuated strain of *Mycobacterium bovis*) reduces the incidence of meningeal and miliary tuberculosis in early childhood. The efficacy against pulmonary tuberculosis is doubtful; the mainstay of the tuberculosis control programme is case-finding and treatment.

WHO recommends that all infants in highly endemic countries should receive a single dose of BCG vaccine as soon as possible after birth. In low-endemic countries, BCG vaccine can be given to infants and children at high risk of tuberculosis exposure. Infants known to be HIV-infected (with or without symptoms) should **not** receive BCG vaccination. Infants born to known HIV-infected mothers should only be immunized if no signs or symptoms suggestive of HIV infection are present and after taking into consideration the likelihood of the infant being infected with HIV, and the potential risk of exposure to tuberculosis. If HIV infection status can be established

with early virological testing, BCG vaccine can be administered once HIV infection has been ruled out.

Infants exposed to smear-positive pulmonary tuberculosis shortly after birth should not receive BCG vaccination until completion of 6 months of prophylactic isoniazid treatment (see section 6.2.4).

BCG vaccine may be given at the same time as other live vaccines, but if not given simultaneously they should be given 4 weeks apart. However, when BCG vaccine is given to infants, there is no need to delay routine primary immunizations.

Powder for injection, live bacteria of a strain derived from the bacillus of Calmette and Guérin.

Uses: active immunization against tuberculosis; see also section 6.2.4.

Contraindications: see introductory notes; also HIV infection (see introductory note above), immunodeficiency, patients receiving immunosuppressive therapy; generalized septic skin conditions.

Precautions: pregnancy (Appendix 2); eczema, scabies (vaccine site must be lesion-free); **interactions:** Appendix 1.

Dose:

Immunization against tuberculosis, *by intradermal injection*, **INFANTS** up to 12 months, 0.05 ml.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: see introductory notes; also rarely lymphadenitis, local ulceration, disseminated BCG infection in immunodeficient individuals, and osteitis.

Cholera vaccine

Cholera is caused by *Vibrio cholerae* and is closely associated with poor sanitation. It is transmitted by faecal contamination of water and food; person-to-person transmission is uncommon. WHO recommends the use of cholera vaccines as a preventative measure but not for containing an outbreak. Immunization with **inactivated oral vaccine** should be considered for populations at imminent risk of a cholera epidemic. In emergency situations, high-risk populations, such as people in crowded refugee camps and urban slums, should be immunized. Immunization for travellers is only recommended for individuals at increased risk of exposure, particularly emergency relief and health-care workers in refugee situations.

Two types of oral cholera vaccines (live and inactivated) are effective for immunization, but only the inactivated vaccine is currently commercially available. Protection is obtained 7 days after completing the course and lasts for at least 6 months, but has not been demonstrated in children less than 2 years of age.

Injectable cholera vaccine is not recommended by WHO because it provides unreliable protection and does not prevent transmission of infection.

Oral suspension, inactivated (WC/rBS) cholera virus.

NOTE. Formulations vary between products and manufacturers and dilution may be required before administration; consult manufacturer's literature

Uses: active immunization against cholera.

Contraindications: see introductory notes; also hypersensitivity to previous dose.

Precautions: see introductory notes.

Dose:

Immunization against cholera, *by mouth*, **ADULT** and **CHILD** over 2 years, 2 doses, separated by 1 week.

Adverse effects: see introductory notes; also mild transient gastrointestinal disturbances reported.

Diphtheria vaccine

Diphtheria is a bacterial infection caused by *Corynebacterium diphtheriae* and is transmitted from person to person through close physical and respiratory contact. Diphtheria vaccine is a formaldehyde-inactivated preparation of the diphtheria toxin, adsorbed onto a mineral carrier to increase its antigenicity and to reduce adverse reactions.

Diphtheria vaccine is given as part of primary immunization schedules in fixed-dose combinations with tetanus, or tetanus and pertussis vaccines. Combinations with other antigens such as *Haemophilus influenzae* type b, poliomyelitis, and hepatitis B vaccines are available in some countries. Immunization against diphtheria should be considered for health-care workers who are at risk of occupational exposure to *Corynebacterium diphtheriae*.

For primary immunization in infants, WHO recommends a 3-dose schedule of a *three-component* preparation of **diphtheria vaccine in combination with pertussis and tetanus vaccines** also known as the DTP or the 3-in-1 vaccine. The first dose is given at 6 weeks of age, followed by 2 further doses, each at minimum intervals of 4 weeks apart. For previously unimmunized children, aged between 1 and 6 years, the recommended schedule is 2 doses, given 2 months apart, and a third dose after 6–12 months. In non-endemic countries, at least 1 booster dose should be given after completion of the primary series. Many national immunization programmes include 1–2 booster doses, for example, one at 2 years of age and a second at 4–7 years of age.

The *two-component* diphtheria with tetanus vaccine exists in 2 forms. The form containing a low dose of diphtheria toxoid is associated with less frequent local reactions in adults and older children than the standard-dose diphtheria preparation. Low-dose diphtheria with tetanus should be used for adults and children aged 7 years and older. When tetanus prophylaxis is needed following tetanus injuries, combined diphtheria and tetanus preparations should be used rather than tetanus alone to promote immunity against diphtheria (see also Tetanus vaccine).

Diphtheria, tetanus, and pertussis vaccine (DTP)

Injection, diphtheria and tetanus toxoids and pertussis vaccine adsorbed onto a mineral carrier.

NOTE. Available with either an acellular pertussis component or a whole cell pertussis component (see also under Pertussis).

Uses: active immunization against diphtheria, tetanus, and pertussis.

Contraindications: see introductory notes.

Precautions: see introductory notes; whole cell pertussis component associated with more frequent minor adverse effects than acellular pertussis component; the frequency increases with age and number of injections and so vaccines containing whole cell pertussis are not recommended for adolescents and adults.

Dose:

Primary immunization of children against diphtheria, pertussis, and tetanus, *by intramuscular injection*, **INFANT** from 6 weeks of age, 3 doses, each of 0.5 ml with an interval of not less than 4 weeks between each dose; **CHILD** 1–6 years of age, 2 doses, each of 0.5 ml separated by an interval of 2 months, followed by a third dose after 6–12 months.

Adverse effects: see introductory notes; minor adverse effects are more frequent with vaccines containing a whole cell pertussis component (see also under Pertussis).

Diphtheria (standard dose) and tetanus vaccine (for children under 7 years)

Injection*, diphtheria (standard dose) and tetanus toxoids adsorbed onto a mineral carrier.*

Uses: active immunization of children under 7 years against diphtheria and tetanus.

Contraindications: see introductory notes.

Precautions: see introductory notes.

Dose:

Primary immunization of children against diphtheria and tetanus, *by intramuscular injection*, **CHILD** under 7 years, 3 doses, each of 0.5 ml, with an interval of not less than 4 weeks between each dose.

Reinforcing immunization of children against diphtheria and tetanus, *by intramuscular injection*, **CHILD** under 10 years,1 dose of 0.5 ml at least 3 years after completion of primary course of diphtheria, pertussis, and tetanus vaccine, or diphtheria and tetanus vaccine.

Adverse effects: see introductory notes.

Diphtheria (low dose) and tetanus vaccine

Injection, diphtheria (low dose) and tetanus toxoid adsorbed onto a mineral carrier.

Uses: active immunization of adults and children aged 7 years and over against diphtheria and tetanus (see note above).

Contraindications: see introductory notes.

Precautions: see introductory notes.

Dose:

Primary immunization of unimmunized adults and children aged 7 years and over against diphtheria and tetanus, *by intramuscular injection*, **ADULT** and **CHILD** 7 years and over, 2 doses, each of 0.5 ml, separated by an interval of 2 months, followed by a third dose after 6–12 months.

Reinforcing immunization of adults and children aged 7 years and over against diphtheria and tetanus, *by intramuscular injection*, **ADULT** and **CHILD** 7 years and over, 1 dose of 0.5 ml, 10 years after completing primary course.

Adverse effects: see introductory notes.

Haemophilus influenzae type b vaccine

Haemophilus influenzae type b (Hib) causes serious infection such as bacterial pneumonia and meningitis, especially in young children. The bacteria are transmitted from person to person by droplets from nasopharyngeal secretions. WHO recommends the inclusion of ***Haemophilus influenzae*** **type b vaccine** in all routine infant immunization programmes. The risk of infection decreases in older children and therefore Hib vaccine is not generally offered to children over 2 years of age. However, older children and adults at an increased risk of Hib infection should be vaccinated, including individuals with HIV or immunoglobulin deficiency, stem cell transplant recipients, patients with malignant neoplasms receiving chemotherapy, and those with asplenia (for example, due to sickle-cell disease or splenectomy).

For primary immunization, a 3-dose series is generally given at the same time as the primary series of diphtheria-tetanus-pertussis (DTP) vaccine. Combination preparations containing *Haemophilus influenzae* type b vaccine with either diphtheria-tetanus-pertussis, hepatitis B, or poliomyelitis vaccines are available.

Injection, capsular polysaccharide of Haemophilus influenzae type b conjugated to a protein carrier

NOTE. Liquid and freeze-dried preparations are available; excipients may vary between individual products and reconstitution may be required before administration (consult manufacturer's information)

Uses: active immunization against *Haemophilus influenzae* type b.

Contraindications: see introductory notes.

Precautions: see introductory notes.

Dose:

Primary immunization against *Haemophilus influenzae* type b, *by intramuscular injection*, **INFANT** 6 weeks–1 year of age, 3 doses, each of 0.5 ml, separated by 4–8 weeks; **ADULT** and **CHILD** over 1 year of age, 1 dose of 0.5 ml.

BOOSTER DOSE. In some countries a booster dose is given between 12 and 18 months of age.

RECONSTITUTION. The vaccine should not be mixed in the vial or syringe with any other vaccine unless it is an approved use or manufactured as a combined product; consult manufacturer's literature for further information.

ADMINISTRATION. The vaccine should be given in the deltoid region in adults and older children; anterolateral thigh is the preferred site in infants and young children; if given as a separate injection at the same time as other vaccines, it should be administered at a different site.

Adverse effects: see introductory notes; also irritability.

Hepatitis A vaccine

Hepatitis A is caused by hepatitis A virus. It is transmitted via the faecal–oral route from person to person through close physical contact and ingestion of contaminated food and water. Those at increased risk of infection include parenteral drug abusers, individuals who change sexual partners frequently, individuals exposed to untreated sewage, those living in closed communities, travellers to endemic countries, laboratory staff working with the virus, patients with haemophilia treated with plasma-derived clotting factors, and individuals who work with primates. Patients with chronic liver disease including chronic hepatitis B or chronic hepatitis C are at risk of severe liver disease if infected with hepatitis A.

In highly endemic countries, exposure is almost universal before 10 years of age and large-scale immunization programmes should not be undertaken. In areas of intermediate endemicity with periodic outbreaks, control of hepatitis A may be achieved through widespread vaccination programmes, but is most successful in small, self-contained communities. In countries with low endemicity, vaccination for high-risk populations may be recommended.

Several vaccines, which provide long-lasting protection, are available but none are licensed for use in children under 1 year of age; the dose of the vaccine and vaccination schedule varies between manufacturers. A single dose of vaccine provides a protective antibody response within a month; most manufacturers recommend a second dose 6–18 months later to ensure long-term protection.

Combined vaccines are available, including inactivated hepatitis A with recombinant hepatitis B vaccine.

Injection, inactivated hepatitis A virus.

Uses: active immunization against hepatitis A.

Contraindications: see introductory notes.

Precautions: see introductory notes.

Dose:

Immunization against hepatitis A, *by intramuscular injection*, **ADULT** and **CHILD** over 1 year of age, single dose; a booster dose can be given 6–18 months after the initial dose.

NOTE. Various formulations of hepatitis A vaccines are available, which may contain different adsorbents or concentrations of antigen. Consult manufacturer's literature for further information about specific dosages, booster intervals, administration, and use in children.

Adverse effects: see introductory notes.

Hepatitis B vaccine

Hepatitis B is caused by 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 haemophiliacs. 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 travellers to endemic countries.

WHO recommends **hepatitis B vaccine** is given as part of the national infant immunization programme. Catch-up immunization should be considered for older age groups, or high-risk individuals who have not been previously immunized in countries with intermediate or low hepatitis B endemicity.

Two types of hepatitis B vaccines are available; plasma-derived and recombinant vaccines. Both types are highly effective but the recombinant vaccine is most commonly used. Hepatitis B vaccine is available as a monovalent or a fixed-combination preparation with other antigens such as *Haemophilus influenzae* type b, poliomyelitis, diphtheria, pertussis, and tetanus. The monovalent vaccine should be used when immunizing infants at birth. Recommended schedules vary considerably between countries, but the minimum recommended interval between doses is 4 weeks. In countries where a high proportion of hepatitis B infections are acquired perinatally, a 3-dose 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 diphtheria-tetanus-pertussis (DTP) or other vaccines.

A reduced immunogenicity of the vaccine may occur in individuals with immunodeficiency including advanced HIV infection, diabetes, chronic liver disease or chronic renal failure.

Injection, inactivated hepatitis B surface antigen adsorbed onto a mineral carrier.

Uses: active immunization against hepatitis B.

Contraindications: see introductory notes.

Precautions: see introductory notes; also diabetes mellitus; chronic renal failure (Appendix 4); and chronic liver disease (Appendix 5) (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 diphtheria-tetanus-pertussis schedule; refer to current WHO advice for hepatitis B vaccine.

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; anterolateral thigh is the preferred site in infants and young children; it should not be injected into the buttock (vaccine efficacy is reduced).

Adverse effects: see introductory notes.

Influenza vaccine

Influenza viruses type A and B are common causes of respiratory illnesses and are transmitted from person to person via droplets or respiratory secretions; their antigenic structure is constantly changing. WHO monitors these changes each year and makes recommendations for inclusion of strains in the influenza vaccines for the following season.

There are various forms of inactivated influenza vaccine available, and live vaccines are licensed for use in some countries. Some vaccines are grown on chick embryos and are therefore contraindicated in individuals hypersensitive to eggs. Split virus vaccines and subunit vaccines show reduced systemic reactogenicity compared with whole virus preparations.

Annual immunization with **inactivated vaccine** is recommended in the elderly and those of any age with diabetes mellitus, chronic heart disease, chronic liver disease, chronic renal disease, chronic respiratory disease including asthma, or

immunosuppression due to disease or drug treatment. Vaccination with inactivated vaccine can be considered for contacts of high-risk people, pregnant women, children between 6 and 23 months of age, health-care workers or other key workers, on the basis of national risk.

Injection, inactivated influenza virus, types A and B.

Uses: active immunization against influenza in individuals at risk.

Contraindications: see introductory notes.

Precautions: see introductory notes; **interactions:** Appendix 1.

Dose:

Immunization against influenza (annually for high-risk persons), *by intramuscular injection*, **ADULT** and **CHILD** over 9 years, 0.5 ml as a single dose; **CHILD** 6–35 months, 0.25 ml as a single dose; **CHILD** 3–9 years, initially 0.5 ml, with a second dose of 0.5 ml after at least 4 weeks if not previously infected or vaccinated.

ADMINISTRATION. The trivalent inactivated influenza vaccine should be given into the deltoid muscle in adults and children over 1 year and the anterolateral aspect of the thigh in infants 6–12 months of age.

Adverse effects: see introductory notes; also myalgia; very rarely Guillain-Barré syndrome has been associated with immunization in older adults.

Japanese encephalitis vaccine

Japanese encephalitis is the leading cause of viral encephalitis in Asia. It is transmitted to humans by mosquitoes from animal hosts (often pigs and water birds) found mostly in rural areas where flooding irrigation is practised. Vaccination against Japanese encephalitis should be considered for endemic populations where it presents a public health problem; the most effective strategy is an immunization catch-up campaign, followed by incorporation of the **Japanese encephalitis vaccine** into the routine immunization programme. Vaccination is also recommended for travellers to endemic areas.

3 types of vaccine are available: the inactivated mouse-brain-derived vaccine based on the Nakayama or Beijing strains, the inactivated cell-culture-derived vaccine based on the Beijing P-3 strain, and the live attenuated cell-culture-derived SA 14-14-2 vaccine; all are suitable for use in children. The recommended immunization schedule varies between vaccines and is dependent on local epidemiology. Individual manufacturer's literature should be consulted for specific information.

Injection, inactivated mouse-brain-derived vaccine, or inactivated cell-culture-derived vaccine, or live attenuated cell-culture-derived SA 14-14-2 vaccine.

NOTE. Formulations, doses, and immunization schedules vary between products and manufacturers; consult individual manufacturer's literature.

Uses: active immunization against Japanese encephalitis.

Contraindications: see introductory notes; immunosuppression (live vaccine); pregnancy (live vaccine; Appendix 2); **interactions:** Appendix 1 (see Vaccine, live).

Precautions: see introductory notes.

Dose:

Primary immunization against Japanese encephalitis (inactivated vaccine), *by subcutaneous injection*, **CHILD** 1–3 years, 2 doses given at intervals of 4 weeks, followed by a booster dose after 1 year.

Primary immunization against Japanese encephalitis (inactivated vaccine), *by subcutaneous injection*, **ADULT** and **CHILD** over 1 year, 1 dose given on days 0, 7, and 28 (total of 3 doses), followed by a booster dose after 1 year; alternatively, 2 doses separated by 1–4 weeks, followed by a booster dose after 1 year.

NOTE. The dose of inactivated vaccine varies between 0.25 ml and 1 ml (doses of 0.25–0.5 ml are usually administered to children under 3 years of age); refer to manufacturer's literature for further information. Subsequent booster doses at 3-year intervals may be recommended for continued protection with the inactivated mouse-brain-derived vaccine up to the age of 10–15 years.

Immunization against Japanese encephalitis (live vaccine), *by subcutaneous injection*, **ADULT** and **CHILD** over 1 year, 1 dose, followed by a single booster dose after 1 year.

Adverse effects: see introductory notes; also headache, myalgia, gastrointestinal disturbances, delayed hypersensitivity reactions (usually within 2 weeks of administration); potentially fatal acute disseminated encephalomyelitis reported with inactivated mouse-brain-derived vaccine.

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. Immunization should be considered for individuals with early signs of HIV-induced immunosuppression in endemic areas or during outbreaks. Large-scale vaccination to control ongoing outbreaks is of limited value, but immunization of high-risk individuals within 2 days of exposure with a measles-containing vaccine may improve the clinical course of measles. A single dose of **measles vaccine** is recommended as part of the primary immunization programme. A second opportunity for measles immunization either through routine or periodic immunization services is also recommended.

Because of the risk of early and severe measles infection, HIV-infected infants (unless severely immunocompromised) should be given the measles vaccine at 6 months of age, followed by an additional dose at 9 months of age.

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 including autism, or chronic bowel disease.

Powder for injection, live, attenuated measles virus.

Uses: active immunization against measles.

Contraindications: see introductory notes.

Precautions: see introductory notes; also pregnancy (Appendix 2); **interactions:** Appendix 1.

Dose:

Primary immunization of children against measles, *by intramuscular* or *subcutaneous injection*, **INFANT** and **CHILD,** 1 dose of 0.5 ml at 9 or 12 months of age; a reinforcing dose of 0.5 ml can be given after 4 weeks or up to 6 years of age.

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: see introductory notes; also local lymphadenopathy, rash; rarely thrombocytopenia purpura.

Measles, mumps and rubella vaccine (MMR vaccine)

Injection, live, attenuated measles virus, mumps virus, and rubella virus.

Uses: active immunization against measles, mumps, and rubella.

Contraindications: see introductory notes; also pregnancy (Appendix 2).

Precautions: see introductory notes; **interactions:** Appendix 1.

Dose:

Primary immunization of children against measles, mumps, and rubella, *by intramuscular* or *subcutaneous injection*, **CHILD** 12–15 months, 1 dose of 0.5 ml; a reinforcing dose of 0.5 ml can be given 2–5 years after the primary dose.

Prophylaxis in susceptible children after exposure to measles, *by intramuscular* or *subcutaneous injection* within 72 hours of contact, **CHILD** 1 year and above, 1 dose of 0.5 ml.

Adverse effects: see introductory notes; adverse reactions are considerably less common after second dose; rash, transient arthralgia and arthritis in adult females; mild parotitis; rarely aseptic meningitis (with some strains of mumps vaccine), orchitis, thrombocytopenic purpura.

Meningococcal meningitis vaccine

Neisseria meningitidis causes meningococcal disease including meningitis and septicaemia and primarily affects young children. The bacteria are transmitted from person to person via respiratory secretions. Immunization against meningococcal disease is recommended as part of the routine childhood immunization programme, for outbreak situations, for individuals at high-risk including those in military camps and boarding schools, travellers to epidemic areas, and for those with a predisposition to meningococcal disease (for example, those with asplenia and inherited immune deficiencies).

Meningococcal vaccines are available as combinations of capsular polysaccharide antigens (serogroups A and C, *or* A, C, W135, and Y) or as a polysaccharide of serogroup C conjugated to a protein carrier; other variants of the vaccine are available in some countries.

Group C conjugate vaccine is recommended for national childhood immunization programmes; for children 2–12 months of age, 3 doses are given at intervals of 4 weeks. A single dose of group C conjugate vaccine is sufficient in children over 12 months of age. However, individuals with asplenia or splenic dysfunction should be given 2 doses, 2 months apart; immunized individuals who develop splenic dysfunction should be given one additional dose.

A single dose of either A and C, *or* A, C, W135, and Y polysaccharide vaccine is recommended to control outbreaks and for at-risk individuals including travellers to epidemic areas. Groups A and C, and A, C, W135, and Y vaccines elicit a suboptimal response in infants under 2 years of age and are not recommended for routine immunization; however, they may given in emergency outbreak situations.

Meningococcal group C conjugate vaccine

Injection, capsular polysaccharide antigen of Neisseria meningitidis serogroup C conjugated to a protein carrier and adsorbed onto a mineral carrier.

NOTE. Both powder for reconstitution and suspension preparations are available.

Uses: active immunization against meningitis and septicaemia caused by *N. meningitidis* serogroup C.

Contraindications: see introductory notes.

Precautions: see introductory notes.

Dose:

Primary immunization against infection by *Neisseria meningitidis* (serogroup C), *by intramuscular injection*, **INFANT** 2–12 months of age, 3 doses, each of 0.5 ml, given at intervals of 4 weeks; **ADULT** and **CHILD** over 1 year, 0.5 ml as a single dose.

RECONSTITUTION. The vaccine should not be mixed in the vial or syringe with any other vaccine unless it is an approved use or manufactured as a combined product. 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; if given as a separate injection at the same time as other vaccines, it should be administered at a different site.

Adverse effects: see introductory notes.

Meningococcal polysaccharide A and C, or A, C, W135, and Y vaccines

Powder for injection, inactivated polysaccharide antigens of Neisseria meningitidis serogroups A and C, or serogroups A, C, W135, and Y.

NOTE. Formulations may vary between products; consult manufacturer's literature for further information regarding individual vaccines.

Uses: active immunization against meningitis and septicaemia caused by *N. meningitidis* serogroups A and C, or serogroups A, C, W135 and Y.

Contraindications: see introductory notes.

Precautions: see introductory notes.

Dose:

Immunization against infection by *N. meningitidis* (serogroups A and C, or A, C, W135, and Y), *by subcutaneous injection,* **ADULT** and **CHILD,** 0.5 ml as a single dose.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: see introductory notes.

Mumps vaccine

Mumps is a mostly a mild childhood disease, but it can also affect adults, in whom complications such as meningitis and orchitis are more common. The mumps virus is transmitted from person to person via airborne droplets.

Mumps vaccine is a live, attenuated vaccine and is available as a single-antigen vaccine or in combination with measles and rubella vaccines. For countries seeking to immunize against mumps, WHO recommends the use of the **combined measles,**

mumps and rubella vaccine (MMR) as part of the national infant immunization programme. 2 doses of mumps vaccine are required for long-term protection; the first dose should be given at 12–18 months of age; the second dose at least 4 weeks later, but before 6 years of age (usually school entry age). See also Measles vaccine above.

NOTE. For combined **measles, mumps and rubella vaccine**, *see* under Measles, mumps and rubella vaccine (MMR) above.

Powder for injection, live attenuated strain of mumps virus.

Uses: active immunization against mumps.

Contraindications: see introductory notes; also pregnancy (Appendix 2); advanced immunodeficiency or immunosuppression.

Precautions: see introductory notes.

Dose:

Immunization of children against mumps, *by subcutaneous injection*, **CHILD,** 1 dose 0.5 ml at 12–18 months of age, followed by a second dose of 0.5 ml at least 4 weeks later or up to 6 years of age.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: see introductory notes; also parotid swelling; rarely orchitis, sensorineural deafness, and aseptic meningitis (higher risk with some specific strains).

Pertussis vaccine

Pertussis (whooping cough) is a bacterial respiratory infection caused by *Bordetella pertussis* and is transmitted through droplets. **Pertussis vaccine** is usually administered in fixed-dose combinations with diphtheria, tetanus and other vaccines as part of the primary immunization programme. WHO recommends 3 doses, given at 6, 10, and 14 weeks of age. Booster doses are recommended 1–6 years after the primary series in countries where the incidence of pertussis has been reduced by immunization. Single component pertussis vaccines are available in some countries.

Whole-cell vaccine composed is frequently associated with minor adverse reactions such as local redness and swelling, fever, and agitation. Prolonged crying and seizures are less common. Local administration site reactions tend to increase with age and number of injections and so whole-cell pertussis vaccine is not recommended for adolescents and adults. An acellular form of the vaccine is also available and can be used for immunization of older children and adults; it has fewer local and systemic effects compared with whole-cell pertussis vaccine (see under Diphtheria).

NOTE. For combined **Diphtheria, pertussis and tetanus vaccine**, *see* under Diphtheria vaccine above.

Pneumococcal vaccine

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. WHO recommends that **pneumococcal conjugate vaccine** should be included in national routine childhood immunization programmes. The 7-valent conjugate vaccine (PCV-7) provides effective protection in young children; the primary schedule usually consists of 3 doses, administered at intervals of at least 4 weeks; other 3-dose schedules have been shown to be effective and are in use in some countries. A booster dose given after 12 months of age may improve the immune response. Immunization should be initiated before 6 months of age and may start as early as 6 weeks of age. The vaccine can be given to HIV-infected individuals.

A single dose of PCV-7 can be given to children aged 12–24 months 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.

Injection, capsular polysaccharides of Streptococcus pneumoniae conjugated to a protein carrier, adsorbed onto a mineral carrier

NOTE. A 7-valent conjugate vaccine is currently available; other multivalent conjugate vaccines are under development

Uses: active immunization against *Streptococcus pneumoniae.*

Contraindications: see introductory notes.

Precautions: see introductory notes.

Dose:

Primary immunization against infection by *Streptococcus pneumoniae* (7-valent conjugate vaccine), *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: see introductory notes.

Poliomyelitis vaccine

Poliomyelitis is an acute viral infection, which causes paralysis of varying degrees. It is transmitted from person to person via the oral–oral or faecal–oral route. Poliomyelitis vaccine should be included in national routine childhood immunization programmes.

Two types of vaccines are available. **Oral poliomyelitis vaccine (OPV)** contains 3 types of live, attenuated poliomyelitis viruses; monovalent live oral vaccines are also available. Injectable inactivated poliomyelitis vaccine (IPV) contains 3 types of inactivated strains.

For primary immunization using OPV, a 3-dose schedule is used. Vaccination may need to be repeated in patients with diarrhoea or vomiting. HIV-infected individuals can receive the live oral vaccine, but it must **not** be used for those with primary immunodeficiency, those who are immunosuppressed, or their close contacts. The need for strict personal hygiene must be stressed as the vaccine virus is excreted in the faeces; the contacts of a recently vaccinated baby should be advised of the need for thorough hand-washing after changing the baby's nappies. Reinforcing doses can be given after primary immunization.

Inactivated poliomyelitis vaccine is used in some countries for routine immunization; routine schedules vary widely, but in industrialized countries, usually include 2–3 doses in the first year of life and at least one booster dose 6–12 months after the last dose of the primary series. Sequential schedules using IPV followed by OPV are also used in some countries to decrease the risk of vaccine-associated poliomyelitis, which occurs only rarely with OPV; usually 1–3 doses of IPV are followed by 2–3 doses of OPV. The inactivated vaccine is available as a monovalent vaccine or in fixed combinations with other antigens.

Countries considering a change from OPV to IPV use should conduct a thorough evaluation of the epidemiological, financial and operational implications before finalizing a change in policy.

Poliomyelitis vaccine (OPV) (live, attenuated)

Oral suspension, live, attenuated poliomyelitis virus, types 1, 2, and 3.

NOTE. Monovalent vaccines are available for use in some countries.

Uses: active immunization against poliomyelitis.

Contraindications: see introductory notes; also primary immunodeficiency or immunosuppression.

Precautions: see introductory notes; also pregnancy (Appendix 2); **interactions:** Appendix 1.

Dose:

Primary immunization of children against poliomyelitis, *by mouth*, **CHILD,** 3 drops at birth and at 6, 10, and at 14 weeks of age. Reinforcing immunization of children against poliomyelitis, *by mouth*, **CHILD,** 3 drops at least 3 years after completion of primary course and a further 3 drops at 15–19 years of age.

Primary immunization of unimmunized adult against poliomyelitis, *by mouth*, **ADULT,** 3 doses, each of 3 drops, with an interval of at least 4 weeks between each dose. Reinforcing immunization of adults against

poliomyelitis, *by mouth*, **ADULT,** 3 drops, 10 years after completion of primary course.

Adverse effects: see introductory notes; rarely, vaccine-associated poliomyelitis in recipients of vaccine and contacts of recipients.

Poliomyelitis vaccine (IPV) (inactivated)

Injection, inactivated poliomyelitis virus, types 1, 2, and 3.

Uses: active immunization against poliomyelitis.

Contraindications: see introductory notes.

Precautions: see introductory notes.

Dose:

Primary immunization of children against poliomyelitis, *by intramuscular injection*, **CHILD,** 3 doses, each of 0.5 ml, separated by at least 4 weeks (either at 6, 10, and 14 weeks of age *or* at 2, 4, and 6 months of age), followed by another dose of 0.5 ml after 6–12 months; further reinforcing doses are given in some countries (for example, at 4–6 years; consult national recommendations).

Primary immunization of unimmunized adults against poliomyelitis, *by intramuscular injection*, **ADULT,** 3 doses, each of 0.5 ml, separated by at least 4 weeks; reinforcing doses can be given (consult national recommendations).

Adverse effects: see introductory notes.

Rabies vaccine

Rabies is a virus transmitted to humans by rabid animals via a bite or a scratch. It is invariably fatal once signs of disease occur. WHO recommends *pre-exposure* immunization of individuals at increased risk of contracting rabies, including those at risk due to occupational exposure (such as laboratory workers, veterinary surgeons, animal handlers and health workers), and people living or travelling to enzootic areas (in such areas, children aged 5–15 years are at particular risk of exposure). **Cell-derived rabies vaccines** are used for both pre-exposure and post-exposure protection. Vaccines of nerve cell tissue origin should **not be used** because they are less potent and are frequently associated with adverse events.

Rabies vaccine is used as part of *post-exposure treatment* to prevent rabies in patients who have been bitten by rabid animals or animals suspected of being rabid. The bite wound or scratch should be thoroughly cleansed. Treatment is dependent upon the individual's immune status and upon the level of risk of rabies in the country concerned (consult national immunization schedule). In certain circumstances, for example, patients with incomplete prophylaxis or unimmunized individuals, *passive immunization* with rabies immunoglobulin can be given (see Rabies immunoglobulin, section 19.2). Post-exposure treatment with rabies vaccine **and** rabies immunoglobulin is necessary for

individuals who are immunocompromised, HIV-positive, taking malaria chemoprophylaxis, or under anaesthesia; antibody response should be monitored.

Rabies vaccine (inactivated)

Injection, inactivated rabies virus prepared in cell culture.

Uses: active immunization against rabies; pre-exposure prophylaxis, post-exposure treatment.

Contraindications: see introductory notes.

Precautions: see introductory notes.

RABIES IMMUNOGLOBULIN. 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:

NOTE. Doses may vary between products (consult manufacturer's literature for further information).

Pre-exposure prophylaxis against rabies, *by intramuscular injection*, **ADULT** and **CHILD,** 3 doses, on days 0, 7, and 28 (day 28 preferable, but administration may be advanced towards day 21 if time is limited); alternatively, *by intradermal injection*, 3 doses, each of 0.1 ml, on days 0, 7, and 28 (administration may be advanced towards day 21 if time is limited).

BOOSTER DOSES. Periodic booster doses are recommended only for individuals whose occupation puts them at continuous or frequent risk of rabies exposure. In such cases, a booster dose should be given at intervals dictated by regular testing for rabies antibodies (a concentration of virus neutralizing antibodies of at least 0.5 IU/ml indicates protection). Where serological testing is unavailable, booster vaccination every 5 years may be an acceptable alternative.

Post-exposure treatment against rabies in unimmunized individuals, *by intramuscular injection,* **ADULT** and **CHILD,** 1 dose given on days 0, 3, 7, 14, and 28 (total of 5 doses); *alternatively,* 2 doses on day 0 (one in each deltoid or thigh), followed by 1 dose on days 7 and 21 (total of 4 doses).

Post-exposure treatment against rabies in unimmunized individuals, *by intradermal injection,* **ADULT** and **CHILD** (8-site regimen), 1 dose of 0.1 ml administered at 8 separate sites on day 0 (one in each upper arm, one in each lateral thigh, one on each side of the suprascapular region, and one on each side of the lower quadrant region of the abdomen), followed by 1 doses of 0.1 ml in each upper arm and each lateral thigh on day 7, and 1 dose of 0.1 ml in one upper arm on days 30 and 90; *alternatively* (2-site regimen), 1 dose of 0.1 ml at 2 sites on days 0, 3, 7, and 28 (total of 8 doses).

Post-exposure treatment against rabies in fully immunized individuals, *by intramuscular* or *intradermal injection,* **ADULT** and **CHILD,** 2 doses, separated by 3 days.

ADMINISTRATION: When administered by intramuscular injection, the vaccine should be given in the deltoid region in adults and children; the anterolateral thigh is the preferred site in children less than 2 years of age.

Adverse effects: see introductory notes; also mild gastrointestinal disturbances, headache, dizziness.

Rotavirus vaccine

Rotaviruses are the most common cause of severe diarrhoea in infants and young children. The virus is transmitted via the faecal–oral route from person to person in close contact or via contaminated fomites. WHO recommends the inclusion of rotavirus vaccination into national immunization programmes in regions where efficacy data suggest a significant public health impact; the clinical efficacy of rotavirus vaccines has so far been demonstrated in the United States of America, Europe, and Latin America.

There are two live **oral attenuated rotavirus vaccines** 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.

The rotavirus vaccine virus is excreted in the faeces and may be transmitted to close contacts; the vaccine should be used with caution in those in close contact with immunosuppressed individuals.

Oral suspension, live, attenuated rotavirus

NOTE. Both monovalent and pentavalent vaccines are available, each with different formulations; the dose and schedule varies between products and reconstitution may be necessary before administration (consult individual manufacturer's literature for further information).

Uses: active immunization against rotavirus infection.

Contraindications: see introductory notes; also immunodeficiency; history or predisposition to intussusception.

Precautions: see introductory notes; 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: see introductory notes; also mild and transient gastrointestinal symptoms.

Rubella vaccine

Rubella is normally a mild childhood disease, which 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). WHO recommends either universal immunization of infants and children through the national immunization programme to eliminate rubella and congenital rubella syndrome, or prevention of congenital rubella syndrome through immunization of women of child-bearing age. Countries seeking to eliminate rubella should ensure that all women of child-bearing age and over 80% of children are immunized.

Rubella vaccine should be given to women of child-bearing 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 one 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.

There are a number of rubella vaccines available, either as single antigen vaccines or combined with measles and mumps vaccines (MMR), or the measles vaccine (MR). In most countries, the vaccine is given as MMR or MR as part of the childhood immunization programme. Most vaccines are based on the live, attenuated RA 27/3 strain of the rubella virus.

NOTE. For combined **measles, mumps and rubella vaccine**, see under Measles vaccine above.

Powder for injection), live attenuated rubella virus.

Uses: active immunization against rubella.

Contraindications: see introductory notes; also untreated active tuberculosis; pregnancy (see also introductory notes; Appendix 2).

Precautions: see introductory notes; **interactions:** Appendix 1.

Dose:

Immunization against rubella, *by subcutaneous injection*, **ADULT** and **CHILD**, 0.5 ml as a single dose.

RECONSTITUTION AND ADMINISTRATION. According to the manufacturer's directions.

Adverse effects: see introductory notes; also rash, lymphadenopathy, paraesthesia; 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, and tetanus vaccine (DPT). The 4th booster dose with a tetanus toxoid-containing vaccine should be given at 4–7 years and the fifth dose during adolescence at 12–15 years. A sixth dose can be given in early adulthood for life-long protection (see also under Diphteria). When tetanus prophylaxis is needed following injury, combined diphtheria and tetanus preparations should be used rather than tetanus alone to promote immunity against diphtheria (see below).

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 child-bearing age may be immunized against tetanus with a single-antigen vaccine.

Wounds are considered to be tetanus-prone if they are sustained either more than 6 hours before surgical treatment of the wound or at any interval after injury and show one or more of the following: a puncture-type wound, a compound fracture, a wound containing foreign bodies, a significant degree of devitalized tissue, clinical evidence of sepsis, contamination with soil/manure likely to contain tetanus organisms. All wounds should receive thorough cleansing.

For *clean wounds,* fully immunized individuals (those who have received a total of 5 doses of tetanus vaccine at appropriate intervals) and those whose primary immunization is complete (with boosters up to date) do not require tetanus vaccine; individuals whose primary immunization is incomplete or whose boosters are not up to date require a reinforcing dose of tetanus vaccine (followed by further doses as required to complete the schedule); non-immunized individuals (or those whose immunization status is not known or who have been immunized but are now immunocompromised) should be given a dose of the vaccine immediately (followed by completion of the full course of the vaccine if records confirm the need).

For *tetanus-prone wounds,* management is as for clean wounds with the addition of a dose of antitetanus immunoglobulin (section 19.2) given at a different site; in fully immunized individuals and those whose primary immunization is complete (see above) the immunoglobulin is needed only if the risk of infection is especially high (for example, contamination with manure). Antibacterial prophylaxis (with benzylpenicillin, or amoxicillin with clavulanic acid, or metronidazole) may also be required for tetanus-prone wounds (see section 6.2).

NOTE. For combined Diphtheria, pertussis and tetanus vaccine, and combined Diphtheria and tetanus vaccines, see under Diphtheria vaccine.

Injection, tetanus toxoid adsorbed onto a mineral carrier.

Uses: active immunization against tetanus and neonatal tetanus; tetanus prophylaxis as part of wound management (tetanus-prone wounds and clean wounds).

Contraindications: see introductory notes.

Precautions: see introductory notes.

ANTITETANUS IMMUNOGLOBULIN. 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:

NOTE. Some countries recommend a maximum of 5 doses of tetanus vaccine in a lifetime.

Primary immunization of unimmunized adolescents and adults (including women of child-bearing 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 (the dose schedule will be dependent upon the immune status of the patient and the level of contamination of the wound; see introductory notes).

Adverse effects: see introductory notes.

Typhoid vaccine

Typhoid fever is caused by *Salmonella typhi.* It is transmitted via the faecal–oral route and associated with poor hygiene and sanitation. Immunization against typhoid fever is recommended for children of school-age and adults in endemic areas, travellers to endemic areas, and laboratory workers handling specimens from suspected cases. The vaccines do not provide complete protection and should not replace hygiene precautions.

A single dose of parenteral Vi capsular polysaccharide vaccine is recommended for adults and children over 2 years of age, followed by booster doses every 3 years in cases of continued exposure.

A live oral typhoid vaccine containing an attenuated strain of *Salmonella typhi* (Ty21a) is available either as enteric coated capsules, or as a liquid suspension. The capsules are licensed for individuals over 5 years of age and are given as 4 doses, each 2 days apart; the suspension can be administered to children over 2 years of age and is given as 3 doses, each 2 days apart. Protection is achieved 7 days after the last dose. In endemic areas, a booster dose of the live oral vaccine is recommended every 3 years; for travellers to endemic areas from non-endemic areas an annual booster is recommended. Oral typhoid vaccine is contraindicated in immunosuppressed individuals and in acute gastrointestinal illness (asymptomatic HIV-positive individuals can be given the vaccine if CD4 cell counts are over 200 mm^3).

Inactivated whole-cell typhoid vaccines may still be available in some countries; children over 5 years of age are given 2 doses separated by an interval of 4 weeks, with a booster dose every 3 years. However, inactivated whole-cell vaccines are associated with frequent adverse effects and WHO recommends that these vaccines should be replaced with either the Vi-based polysaccharide vaccine or live oral vaccines.

Capsule, live attenuated strain of Salmonella typhi (Ty21a)

Oral suspension, live attenuated strain of Salmonella typhi (Ty21a)

Injection, Vi capsular polysaccharide typhoid: 25 microgram/0.5 ml

NOTE. Reconstitution of the oral suspension may be necessary before administration (consult individual manufacturer's literature for further information).

Uses: active immunization against typhoid.

Contraindications: see introductory notes.

Precautions: see introductory notes; **interactions:** Appendix 1.

Dose:

Immunization against typhoid fever, *by mouth*, capsules, **ADULT** and **CHILD** over 5 years, one dose given on days 1, 3, 5, and 7 (total of 4 doses); *suspension*, **ADULT** and **CHILD** over 2 years, one dose given on days 1, 3, and 5 (total of 3 doses); reinforcing doses can be given every year for travellers to disease-endemic countries and every 3 years for those living in disease-endemic areas.

ADMINISTRATION WITH ANTIBACTERIALS AND ANTIMALARIALS. Administration of oral typhoid vaccine should be coordinated so that the antimalarial, mefloquine, is not taken for at least 12 hours before or after a dose; vaccination should be completed at least 3 days before the first dose of mefloquine or other antimalarials (except proguanil hydrochloride in combination with atovaquone, which may be given concomitantly). Oral typhoid vaccine is inactivated by concomitant administration of antibacterials; if possible antibacterials should be avoided 3 days before, or 3 days after, vaccination.

Immunization against typhoid fever (Vi capsular polysaccharide vaccine), *by subcutaneous* or *intramuscular injection*, **ADULT** and **CHILD** 2 years and over, 1 dose of 0.5 ml, with reinforcing doses every 3 years for those at continued risk.

Adverse effects: see introductory notes.

Varicella vaccine

Varicella-zoster (chickenpox) is a highly contagious disease caused by varicella-zoster virus. Transmission is via droplets, aerosol or direct person-to-person contact. Various formulations of the live, attenuated vaccine based on the Okastrain are available. Varicella-zoster vaccine may be used as part of a national childhood immunization programme. The vaccine may also be used in adolescents or adults without a history of varicella but who are at increased risk of infection.

A single dose of vaccine is effective in children aged 1–12 years; (however, the optimal age for immunization is 12–24 months). In adults and adolescents over 13 years of age, 2 doses, each separated by 4–8 weeks, can be given. In some countries, 1 dose is considered sufficient regardless of age. Post-exposure vaccination can be considered for seronegative health-care workers who come into direct contact with patients with varicella-zoster.

Rarely, the varicella-zoster vaccine virus has been transmitted from vaccinated individuals to close contacts; if a vaccine-related rash develops within 4–6 weeks, contact with varicella-susceptible pregnant women and individuals at high risk of severe varicella infection, including patients with immunodeficiency or receiving immunosuppressive therapy, should be avoided.

Injection, live, attenuated varicella-zoster virus.

Uses: active immunization against varicella-zoster.

Contraindications: see introductory notes; also pregnancy (avoid pregnancy for 3 months after vaccination; Appendix 2); immunodeficiency; patients receiving immunosuppressive therapy; untreated active tuberculosis.

Precautions: see introductory notes; also family history of congenital immune disorders.

Dose:

Immunization against varicella-zoster infection, *by subcutaneous injection*, **ADULT** and **ADOLESCENT** over 13 years of age, 2 doses, each of 0.5 ml, separated by 4–8 weeks; **CHILD** 1–12 years of age, 0.5 ml as a single dose.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: see introductory notes; also mild varicella-like rash within 4–6 weeks.

Yellow fever vaccine

Yellow fever is a viral haemorrhagic fever which is endemic in tropical regions of Africa and South America. The disease is transmitted by *Haemagogus* and *Aedes* mosquito bites. Yellow fever 17D vaccine is a live, attenuated vaccine, which offers protection from 10 days after vaccination, for at least 10 years.

WHO recommends that all countries with endemic yellow fever should incorporate yellow fever vaccine into their national immunization programme; the vaccine should be given to infants at 9–12 months of age and can be given at the same time as the measles vaccine. Yellow fever vaccine is also recommended for people at high risk of yellow fever exposure, including forestry and agricultural workers, and people living in or travelling to endemic areas. During epidemics, mass vaccination campaigns should be initiated as early as possible.

Immunization is **not** recommended for infants aged 6–8 months or during pregnancy, except during an epidemic when the risk of transmission may be very high. Yellow fever vaccine is contraindicated in individuals with severe immunodeficiency or severe egg allergy (HIV-infected individuals may be vaccinated if CD4 cell counts are over 200 per mm^3).

Powder for injection, live, attenuated yellow fever virus.

Uses: active immunization against yellow fever.

Contraindications: see introductory notes; also not recommended for infants under 9 months of age.

Precautions: see introductory notes; also pregnancy (Appendix 2); **interactions:** Appendix 1.

Dose:

Immunization of children against yellow fever, *by deep subcutaneous* or *intramuscular injection*, **INFANT** at 9–12 months, 0.5 ml as a single dose.

Immunization of travellers and other at-risk individuals against yellow fever, *by deep subcutaneous* or *intramuscular injection*, **ADULT** and **CHILD** over 9 months, 0.5 ml as a single dose.

NOTE. Subcutaneous route is preferred.

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions.

Adverse effects: see introductory notes; also headache, myalgia, weakness; very rarely encephalitis (infants more susceptible); viscerotropic disease, multiple organ failure (the elderly more susceptible).

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 anaesthesia. They should never be given until it is certain that general anaesthesia 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 apnoea.

Alcuronium is a non-depolarizing muscle relaxant with a duration of action of about 30 minutes. Its effects may be rapidly reversed after surgery by the anticholinesterase, neostigmine (see below), provided atropine (section 1.3) is given to prevent excessive autonomic activity. **Vecuronium**, another widely used non-depolarizing muscle relaxant, has a shorter duration of action (20–30 minutes); it causes minimal adverse cardiovascular effects.

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 alcuronium and 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 diarrhoea, abdominal cramps, and excess salivation, and so 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 because of 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 (section 8.1) may allow a dose reduction of both the corticosteroid and of the anticholinesterase.

Alcuronium

Injection: 5 mg (chloride)/ml in 2-ml ampoule.

Alcuronium is a representative non-depolarizing muscle relaxant. Various medicines can serve as alternatives.

Uses: muscle relaxation during surgery.

Contraindications: respiratory insufficiency or pulmonary disease; dehydrated or severely ill patients; myasthenia gravis or other neuromuscular disorders.

Precautions: renal impairment (Appendix 4); hepatic impairment (Appendix 5); burns patients (possibly increase dose); electrolyte disturbances; respiratory acidosis or hypokalaemia (possibly decrease dose); history of asthma; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose: Muscle relaxation, *by intravenous injection*, **ADULT,** initially 200–250 micrograms/kg, then 30–50 micrograms/kg as required for maintenance; **CHILD,** initially 125–200 micrograms/kg, then 50 micrograms/kg for maintenance.

Adverse effects: histamine release, leading to allergic reactions, such as wheal and flare effects at site of injection, flushing, and bronchospasm (anaphylactoid reactions reported); transient hypotension, slight increase in heart rate or decreased pulse rate.

Neostigmine

Injection: 500 micrograms in 1-ml ampoule; 2.5 mg (metilsulfate) in 1-ml ampoule.
Tablet: 15 mg (bromide).

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 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

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 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, diarrhoea; signs of overdosage 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.

Pyridostigmine

Injection: 1 mg in 1-ml ampoule.
Tablet: 60 mg (bromide).

Pyridostigmine bromide is a complementary list cholinesterase inhibitor.

Uses: myasthenia gravis.

Contraindications: recent intestinal or bladder surgery; mechanical intestinal or urinary tract obstruction; after suxamethonium; pneumonia; peritonitis.

Precautions: asthma; urinary tract infection; cardiovascular disease including arrhythmias (especially bradycardia or atrioventricular block); hyperthyroidism; hypotension; peptic ulcer; epilepsy; parkinsonism; avoid intravenous injection; renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Myasthenia gravis, *by mouth*, **ADULT,** initially 30–120 mg at suitable intervals throughout the day, gradually increased until desired response is obtained; usual total daily dose within range, 0.3–1.2 g, given at appropriate intervals when high doses are required (doses above 450 mg daily are not usually advisable in order to avoid acetylcholine receptor down regulation); **CHILD** up to 6 years, initially 30 mg; **CHILD** 6–12 years, initially 60 mg; usual total daily dose, 30–360 mg given in divided doses at appropriate intervals.

Myasthenia gravis, *by intramuscular injection*, **ADULT,** 2 mg every 2–3 hours; **NEONATE,** 50–150 micrograms daily, before feeds (but neostigmine usually preferred); **CHILD**, 1–12 mg daily, given in divided doses at appropriate intervals.

Adverse effects: muscarinic effects generally weaker than those associated with neostigmine; and include increased salivation, nausea and vomiting, abdominal cramps, and diarrhoea; signs of overdosage 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; rash associated with tablet (bromide salt) formulations.

Suxamethonium

Injection: 50 mg (chloride)/ml in 2-ml ampoule.
Powder for injection (chloride) in vial.

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 hyperkalaemia); 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); hyperkalaemia.

Precautions: digitalis toxicity or recent digitalization; cardiac, respiratory or neuromuscular disease; paraplegia, spinal cord injury, or severe trauma; severe sepsis (risk of hyperkalaemia); prolonged apnoea on repeated injection (infusion preferred for long surgical procedures); hepatic impairment (Appendix 5); renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); children; **interactions:** Appendix 1.

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/minute of solution containing 1–2 mg/ml; maximum, 500 mg/hour; **CHILD,** reduce infusion rate according to body weight.

Adverse effects: postoperative muscle pain, particularly in patients ambulant after operation in females; myoglobinuria; myoglobinaemia; prolonged apnoea; increased intraocular pressure; hyperkalaemia; bradycardia, hypotension, and arrhythmias, particularly with halothane (but, with repeated doses, tachycardia, and 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).

Vecuronium

Powder for injection: 10 mg (bromide) in vial.

Vecuronium is a representative non-depolarizing muscle relaxant. Various medicines can serve as alternatives.

Vecuronium is a complementary list non-depolarizing muscle relaxant.

Uses: muscle relaxation during surgery.

Contraindications: respiratory insufficiency or pulmonary disease; dehydrated or severely ill patients; myasthenia gravis or other neuromuscular disorders.

Precautions: hepatic impairment (Appendix 5); burns patients (possibly increase dose); electrolyte disturbances; respiratory acidosis or hypokalaemia (possibly decrease dose); history of asthma; severe obesity (may require maintenance of adequate airway and ventilation support); pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Intubation, *by intravenous injection*, **ADULT** and **CHILD** over 5 months, initially 80–100 micrograms/kg; usual maintenance dose, 20–30 micrograms/kg; **CHILD** 1–4 months, initially 10–20 micrograms/kg, followed by incremental doses according to response.

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

Muscle relaxation, *by intravenous infusion*, **ADULT**, initially, 40–100 micrograms/kg, then 0.8–1.4 micrograms/kg/minute.

Adverse effects: minimal release of histamine; rarely hypersensitivity reactions including bronchospasm, hypotension, tachycardia, oedema, erythema, and pruritus).

SECTION 21:
Ophthalmological preparations

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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 the 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.

Eye drops 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 eye drops are required at the same time, dilution and overflow may occur if one immediately follows the other; an interval of at least five minutes should therefore be allowed between the two applications.

Systemic absorption, which may occur after topical application of eye drops, can be minimized by using the finger to compress the lacrimal sac at the medial canthus for at least one 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 eye drops 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 gonorrhoea* 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. gonorrhoea*, 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. gonorrhoea* and *C. trachomatis*.

Aciclovir

Ointment: 3% W/W.

Uses: keratitis caused by herpes simplex; systemic herpes simplex infections (section 6.4.1).

ADMINISTRATION. Herpes simplex keratitis, *apply* directly to the eye, **ADULT** and **CHILD,** 1 cm of ointment 5 times daily; 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.

Gentamicin

Solution (eye drops): 0.3% (sulfate).

Gentamicin is a representative ophthalmic antibacterial. Various medicines can serve as alternatives.

Uses: blepharitis; bacterial conjunctivitis; systemic bacterial infections (section 6.2.2).

Contraindications: 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.

Tetracycline

Eye ointment: 1% (hydrochloride).

Tetracycline is a representative ophthalmic antibacterial. Various medicines can serve as alternatives.

Uses: superficial bacterial infection of the eye; mass treatment of trachoma in endemic areas; prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to *Neisseria gonorrhoea* or *Chlamydia trachomatis*.

Contraindications: hypersensitivity to tetracycline group of antibiotics.

Precautions: prolonged use may lead to overgrowth of non-susceptible organisms.

Administration:

Superficial bacterial infection, *apply* directly to the eye, **ADULT** and **CHILD** aged over 8 years, 1 application of ointment 3–4 times daily.

Prophylaxis of neonatal conjunctivitis, *apply* 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, *apply* 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, *apply* 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 a 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

Solution (eye drops): 0.5% (sodium phosphate).

Prednisolone is a representative ophthalmic corticosteroid. Various drugs can serve as alternatives.

Uses: short-term local treatment of inflammation of the eye; malignant disease (section 8.3); suppression of inflammatory and allergic reactions (sections 3 and 18.1).

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.

Administration:

NOTE. Use only under the supervision of an ophthalmologist.

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 anaesthetics

Topical local anaesthetics 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 anaesthesia which lasts for 15 minutes or more. Prolonged or unsupervised use of tetracaine is not recommended.

Tetracaine

Solution (eye drops): 0.5% (hydrochloride).

Also known as Amethocaine.

Tetracaine is a representative ophthalmic local anaesthetic. Various drugs can serve as alternatives.

Uses: short-acting local anaesthesia of the cornea and conjunctiva.

Contraindications: hypersensitivity to ester-type local anaesthetics; 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 anaesthesia, *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 humour, 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 humour by the ciliary body, or increasing the outflow of the aqueous humour 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 humour. 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 airways 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 humour 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

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); hypokalaemia, hyponatraemia, hyperchloraemic acidosis; renal impairment (Appendix 4); severe hepatic impairment (Appendix 5).

Precautions: the elderly; pregnancy (Appendix 2) and breastfeeding (Appendix 3); diabetes mellitus; pulmonary obstruction; monitor blood count and electrolytes if used for long periods; **interactions:** Appendix 1.

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, diarrhoea, taste disturbances; loss of appetite, paraesthesia, flushing, headache, dizziness, fatigue, irritability, depression; thirst, polyuria; reduced libido; metabolic acidosis and electrolyte disturbances on long-term therapy; occasionally drowsiness, confusion, hearing disturbances, urticaria, melaena, glycosuria, haematuria, abnormal liver function, renal calculi, blood disorders (including agranulocytosis and thrombocytopenia), and rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis); transient myopia reported.

Pilocarpine

Solution (eye drops): 2%; 4% (hydrochloride or nitrate).

Pilocarpine is a representative miotic. Various medicines can serve as alternatives.

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 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, browache; conjunctival vascular congestion, superficial keratitis, vitreous haemorrhage, and increased pupillary block reported; lens opacities (following prolonged use); rarely systemic effects including hypertension, tachycardia, bronchial spasm, pulmonary oedema, salivation, sweating, nausea, vomiting, and diarrhoea.

Timolol

Solution (eye drops): 0.25%; 0.5% (as maleate).

Timolol is a representative ophthalmic beta-blocker. Various medicines can serve as alternatives.

Uses: ocular hypertension; chronic open-angle glaucoma, aphakic glaucoma, some secondary glaucomas.

Contraindications: uncontrolled heart failure, bradycardia, heart block; asthma or history of obstructive airways disease (see introductory note above).

Precautions: elderly (risk of keratitis); in angle-closure glaucoma, use with a miotic, and not alone; **interactions:** Appendix 1.

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, paralyse the pupillary constrictor muscles causing dilation of the pupil (mydriasis) and paralyse the ciliary muscles resulting in paralysis of accommodation (cycloplegia). Mydriasis may precipitate acute angle-closure glaucoma particularly in the elderly or long-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 humour 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

Solution (eye drops): 0.1%; 0.5%; 1% (sulfate).

Uses: iritis, uveitis; cycloplegic refraction procedures; premedication (section 1.3); organophosphate poisoning (section 4.2).

Contraindications: angle-closure glaucoma.

Precautions: use may precipitate acute attack of angle-closure glaucoma, particularly in the elderly or long-sighted; infants under 3 months (risk of systemic effects with eye drops; 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, hyperaemia, oedema, and conjunctivitis (on prolonged administration); contact dermatitis; systemic toxicity (in the very young and the elderly).

Epinephrine (adrenaline)

Solution (eye drops): 2% (as hydrochloride).

Epinephrine is a complementary list medicine for use as a mydriatic when medicines in the main list cannot be made available.

Uses: chronic open-angle glaucoma, ocular hypertension (section 21.4); anaphylaxis (section 3); cardiac arrest (section 12.2).

Contraindications: angle-closure glaucoma, unless an iridectomy has been carried out.

Precautions: hypertension, heart disease, aneurysm, arrhythmia, tachycardia, hyperthyroidism, cerebral arteriosclerosis, diabetes mellitus.

Administration:

Chronic open-angle glaucoma, *by ocular instillation*, **ADULT,** 1 drop (0.5% or 1% solution) 1–2 times daily.

Adverse effects: stinging, blurred vision, photophobia, eye pain, conjunctival hyperaemia, headache or browache; occasionally conjunctival sensitization and local skin reactions; conjunctival pigmentation and macular oedema in aphakia (after prolonged use); systemic adverse reactions are rare following topical use at normal dosage but tachycardia, hypertension, arrhythmia, dizziness, and sweating have been reported.

SECTION 22:
Oxytocics and antioxytocics

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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 labour and in the control of postpartum haemorrhage, and the beta$_2$-adrenoceptor agonists, which are used to relax the uterus and prevent premature labour.

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 and is culturally acceptable. Medical abortion may be induced by the sequential use of a single oral dose of **mifepristone** 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 and, therefore when used together with misoprostol, abortion occurs in a shorter time and with a lower dose of the prostaglandin.

Induction and augmentation of labour

Prostaglandins, including **misoprostol**, are effective for the induction of labour. 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 caesarean section.

Postpartum haemorrhage

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 haemorrhage since it is more stable than

ergometrine. However, ergometrine may be used if oxytocin is not available or in emergency situations.

Ergometrine

Injection: 200 micrograms (hydrogen maleate) in 1-ml ampoule.

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.

Uses: prevention and treatment of postpartum and post-abortion haemorrhage in emergency situations and where oxytocin not available.

Contraindications: induction of labour; first and second stages of labour; vascular disease, severe cardiac disease especially angina pectoris; severe hypertension; severe renal and hepatic impairment; sepsis; eclampsia.

Precautions: cardiac disease, hypertension, hepatic impairment (Appendix 5); renal impairment (Appendix 4); multiple pregnancy, porphyria; **interactions:** Appendix 1.

Dose:

Prevention and treatment of postpartum haemorrhage, *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.

Adverse effects: nausea, vomiting, headache, dizziness, tinnitus, abdominal pain, chest pain, palpitations, dyspnoea, bradycardia, transient hypertension, vasoconstriction; stroke, myocardial infarction and pulmonary oedema also reported.

Mifepristone + misoprostol

Tablet 200 mg - tablet 200 micrograms.

Mifepristone is a complementary list medicine for medical termination of pregnancy of up to 63 days gestation where this is permitted under national law and where culturally acceptable.

Uses: medical termination of intrauterine pregnancy of up to 63 days gestation with misoprostol.

Contraindications: uncontrolled severe asthma; suspected ectopic pregnancy (use other specific means of termination); chronic adrenal failure, porphyria.

Precautions: if treatment fails, it is essential that pregnancy is terminated by another method; asthma (avoid if severe); haemorrhagic disorders and anticoagulant therapy; prosthetic heart valve or history of endocarditis (antibacterial prophylaxis recommended); smokers aged over 35 years (increased risk of cardiovascular events); adrenal suppression (may require treatment with a corticosteroid); not recommended in hepatic or renal impairment; breastfeeding (Appendix 3); avoid use of acetylsalicylic acid (aspirin) and non-steroidal anti-inflammatory medicines for analgesia; **interactions**: Appendix 1.

IMPORTANT. For warnings relating to the use of misoprostol in a patient undergoing induction of abortion with a combination of mifepristone and misoprostol, see under Misoprostol.

Dose:

Medical termination of intrauterine pregnancy of up to 63 days gestation, *by mouth*, **ADULT** and **ADOLESCENT,** mifepristone, 200 mg as a single dose, followed 36–48 hours later (unless abortion already complete) by misoprostol, 800 micrograms *vaginally* 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 essential that pregnancy terminated by another method).

NOTE. Careful monitoring essential for 6 hours after the administration of misoprostol (risk of hypotension).

Adverse effects: nausea, vomiting, gastrointestinal cramps; uterine contractions, vaginal bleeding (sometimes severe); less commonly hypersensitivity reactions including rash, urticaria, and facial oedema; rarely malaise, headache, fever, hot flushes, dizziness, chills.

Misoprostol is a complementary drug for medical termination of pregnancy of up to 63 days gestation where this is permitted under national law and where culturally acceptable, and for induction of labour.

Uses: induction of labour; with mifepristone, medical termination of intrauterine pregnancy of up to 63 days gestation.

Contraindications:

INDUCTION OF LABOUR. Placenta praevia or unexplained vaginal bleeding during pregnancy, ruptured membranes, major cephalopelvic disproportion or fetal malpresentation, history of caesarean section or major uterine surgery, untreated pelvic infection, fetal distress, grand multiparas and multiple pregnancy, history of difficult or traumatic delivery.

MEDICAL TERMINATION OF PREGNANCY. See under Mifepristone.

Precautions: conditions where hypotension might precipitate severe complications (for example cerebrovascular disease, cardiovascular disease)

MEDICAL TERMINATION OF PREGNANCY. History of caesarean section or major uterine surgery, grand multiparas (risk of rupture).

IMPORTANT. For warnings relating to use of mifepristone in a patient undergoing induction of abortion with misoprostol, see under Mifepristone.

Dose:

Induction of labour, *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 labour 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, under close medical supervision, *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 essential that pregnancy 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 labour, low-dose vaginal tablets should be used, but if these are not available, 100-microgram oral tablets can be divided to the required dose and administered vaginally.

Adverse effects: uterine hyperstimulation, uterine rupture, fetal distress; less commonly in obstetric setting diarrhoea, abdominal pain, dyspepsia, flatulence, nausea and vomiting, rash, dizziness.

Misoprostol

Vaginal tablet: 25 micrograms.

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 where it is culturally acceptable, and for induction of labour.

Uses: induction of labour; medical termination of intrauterine pregnancy of up to 63 days gestation with mifepristone.

Contraindications:

INDUCTION OF LABOUR. Placenta praevia or unexplained vaginal bleeding during pregnancy, ruptured membranes, major cephalopelvic disproportion or fetal malpresentation, history of caesarean section or major uterine surgery, untreated pelvic infection, fetal distress, grand multiparas and multiple pregnancy, history of difficult or traumatic delivery.

MEDICAL TERMINATION OF PREGNANCY. See under Mifepristone.

Precautions: induction of labour conditions where hypotension might precipitate severe complications (for example, cerebrovascular disease or cardiovascular disease).

MEDICAL TERMINATION OF PREGNANCY. History of caesarean section or major uterine surgery, grand multiparas (risk of rupture).

IMPORTANT. For warnings relating to the use of mifepristone in a patient undergoing induction of abortion with a combination of misoprostol and mifepristone, see under Mifepristone.

Dose:

Induction of labour, *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 labour 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 essential that pregnancy 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 labour, low-dose vaginal tablets should be used, but if these are not available, 100-microgram oral tablets [not included on the 15th WHO Model List] can be divided to the required dose and administered vaginally.

Adverse effects: uterine hyperstimulation, uterine rupture, fetal distress; less commonly in obstetric setting diarrhoea, abdominal pain, dyspepsia, flatulence, nausea and vomiting, rash, dizziness.

Oxytocin

Injection: 10 IU in 1-ml ampoule.

Uses: routine prevention and treatment of postpartum and post-abortion haemorrhage; induction of labour.

Contraindications: hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress; any condition where spontaneous labour or vaginal delivery inadvisable; avoid prolonged administration in oxytocin-resistant

uterine inertia, in severe pre-eclamptic toxaemia, or in severe cardiovascular disease; major cephalopelvic disproportion.

Precautions: induction or enhancement of labour in presence of borderline cephalopelvic disproportion (avoid if significant); mild to moderate pregnancy-associated hypertension or cardiac disease; age over 35 years; history of low-uterine segment caesarean section; avoid tumultuous labour if fetal death or meconium-stained amniotic fluid (risk of amniotic fluid embolism) occurs; water intoxication and hyponatraemia (avoid large volume infusions and restrict fluid intake); caudal block anaesthesia (risk of severe hypertension due to enhanced vasopressor effect of sympathomimetics); **interactions:** Appendix 1.

Dose:

Induction of labour, *by intravenous infusion*, **ADULT** and **ADOLESCENT**, initially 0.001–0.002 IU/minute increased in 0.001–0.002 IU/minute increments at intervals of 30 minutes until up to 3–4 contractions occur every 10 minutes; maximum rate, 0.02 IU/minute.

NOTE. The dose shown above is suitable for use in 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, World Health Organization, 2000).

IMPORTANT. Careful monitoring of fetal heart rate and uterine motility is essential for dose titration (avoid bolus intravenous injection during labour); discontinue immediately in uterine hyperactivity or fetal distress.

Prevention of postpartum haemorrhage, *by intramuscular injection*, **ADULT** and **ADOLESCENT,** 10 IU when the anterior shoulder is delivered or immediately after birth.

Prevention of postpartum haemorrhage, *by slow intravenous injection*, **ADULT** and **ADOLESCENT,** 5 IU when the anterior shoulder is delivered or immediately after birth.

Treatment of postpartum haemorrhage, *by slow intravenous injection*, **ADULT** and **ADOLESCENT,** 5–10 IU or *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/minute; this should be started after the placenta is delivered.

NOTE. For further details on management of postpartum haemorrhage consult *Managing complications in pregnancy and childbirth: A guide for midwives and doctors*. Geneva, World Health Organization, 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 haemorrhage) may cause water intoxication with hyponatraemia. To avoid this, use electrolyte-containing

diluent (not glucose), increase oxytocin concentration to reduce fluid, and restrict fluid intake 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 hyponatraemia (with high doses and large-volume infusions); nausea, vomiting, arrhythmias, rash and anaphylactoid reactions also reported.

22.2 Antioxytocics (tocolytics)

Premature labour

Nifedipine, a dihydropyridine calcium-channel blocker which relaxes the uterus, can be used to postpone labour in uncomplicated cases of premature labour. 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

Immediate release capsule: 10 mg.

Uses: uncomplicated premature labour between 24–33 weeks gestation.

Contraindications: cardiogenic shock; advanced aortic stenosis; within 1 month of myocardial infarction; unstable or acute attacks of angina; porphyria.

Precautions: stop if ischaemic pain occurs shortly after starting treatment; poor cardiac reserve; heart failure or significantly impaired left ventricular function; severe hypotension; hepatic impairment (reduce dose; Appendix 5); diabetes mellitus; breastfeeding (Appendix 3); avoid grapefruit juice (may affect nifedipine metabolism); **interactions:** Appendix 1.

Dose:

Premature labour, *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.

Adverse effects: headache, flushing, dizziness, lethargy; tachycardia, palpitations; exaggerated fall in blood pressure and reflex tachycardia (may lead to myocardial or cerebrovascular ischaemia); gravitational oedema; rash

(erythema multiforme reported), pruritus, urticaria; nausea, constipation or diarrhoea; increased frequency of micturition; eye pain, visual disturbances; gum hyperplasia; asthenia, paraesthesia, myalgia, tremor, gynaecomastia; depression, telangiectasis, cholestasis, and jaundice reported.

SECTION 23:
Peritoneal dialysis solution

Solutions for peritoneal dialysis are preparations for intraperitoneal use which contain electrolytes in a similar concentration 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, haemodialysis is the preferred method to correct the accumulation of toxins, electrolytes, and fluid. Peritoneal dialysis is less efficient than haemodialysis, 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 centre. 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 (of appropriate composition)

Parenteral solution.

Intraperitoneal dialysis solution is a complementary list preparation.

Uses: to correct electrolyte imbalance and fluid overload, and to remove metabolites, in renal failure.

Contraindications: abdominal sepsis; previous abdominal surgery; severe inflammatory bowel disease.

Precautions: care is required with technique to reduce risk of infection; warm dialysis solution to body temperature before use; some drugs may be removed by dialysis.

Dose:

Individualized according to clinical condition, and based on blood results.

Adverse effects: infection including peritonitis; hernia; haemoperitoneum; hyperglycaemia, protein malnutrition; blocked catheter.

SECTION 24:
Psychotherapeutic medicines

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24.1 Medicines used in psychotic disorders

Treatment of psychotic disorders including schizophrenia is both pharmacological and psychosocial. Individual and community programmes 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 (see note below), 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; and
- *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.

NEUROLEPTIC MALIGNANT SYNDROME. 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 by electrolyte defects, and by giving bromocriptine [not included on the 15th WHO Model List] and sometimes dantrolene [not included on the 15th WHO Model List].

Chlorpromazine

Injection: 25 mg (hydrochloride/ml in 2-ml ampoule.
Oral liquid: 25 mg (hydrochloride/5 ml.
Tablet: 100 mg (hydrochloride).

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.

Uses: schizophrenia and other psychotic disorders, mania, psychomotor agitation and violent behaviour; adjunct in severe anxiety.

Contraindications: impaired consciousness due to central nervous system depression; bone marrow depression; phaeochromocytoma.

Precautions: cardiovascular and cerebrovascular disorders; respiratory disease; parkinsonism; epilepsy; acute infections, pregnancy (Appendix 2); breastfeeding (Appendix 3); renal impairment (avoid if severe; Appendix 4); hepatic impairment (avoid if severe; Appendix 5); 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 1.

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery or driving.

Dose:

Schizophrenia and other psychoses, mania, psychomotor agitation, violent behaviour, 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) third to half adult dose;

CHILD (childhood schizophrenia and autism) 1–5 years, 500 micrograms/kg every 4–6 hours (maximum 40 mg daily); **CHILD** 6–12 years, third to half adult dose (maximum 75 mg daily).

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, maximum, 40 mg daily; 6–12 years, maximum, 75 mg daily) (see also Precautions and 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, galactorrhoea, gynaecomastia, impotence, weight gain; sensitivity reactions such as agranulocytosis, leukopenia, leukocytosis, haemolytic anaemia, 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

Injection: 25 mg (decanoate or enantate) in 1-ml ampoule.

Fluphenazine is a representative depot antipsychotic for use when compliance unlikely to be reliable. Various medicines can serve as alternatives.

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; phaeochromocytoma; marked cerebral artherosclerosis.

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 2); breastfeeding (Appendix 3); renal impairment (avoid if severe; Appendix 4); hepatic impairment (avoid if severe; Appendix 5); history of jaundice; leukopenia (monitor blood counts if unexplained fever or infection occur); hypothyroidism; myasthenia gravis; prostatic hypertrophy; angle-closure glaucoma; the elderly (reduce dose in very hot or very cold weather); **interactions:** Appendix 1.

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, oedema.

Haloperidol

Injection: 5 mg in 1-ml ampoule.
Tablet: 2 mg; 5 mg.

Haloperidol is a representative antipsychotic. Various medicines can serve as alternatives.

Uses: schizophrenia and other psychotic disorders, mania, short-term adjunctive management of psychomotor agitation, violent behaviour, and severe anxiety.

Contraindications: impaired consciousness due to central nervous system depression; bone marrow depression; phaeochromocytoma; porphyria; basal ganglia disease.

Precautions: cardiovascular and cerebrovascular disorders, respiratory disease, parkinsonism, epilepsy, acute infections, pregnancy (Appendix 2), breastfeeding (Appendix 3), renal and hepatic impairment (avoid if severe; Appendices 4 and 5), history of jaundice, leukopenia (blood count required if unexplained fever or infection); hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; also subarachnoid haemorrhage and metabolic disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia; the 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 1.

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 behaviour, and severe anxiety, *by mouth*, **ADULT,** 1.5–3 mg 2–3 times daily (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 (maximum, 10 mg daily).

Acute psychotic conditions, *by intramuscular injection*, **ADULT,** initially 2–10 mg (half of the adult dose in elderly or debilitated patients; up to 18 mg in severely affected patients); subsequent doses every 4–8 hours according to response (up to every hour if necessary) up to a maximum of 18 mg daily; **CHILD,** not recommended.

Adverse effects: as for Chlorpromazine (see above), but less sedative effects and fewer hypotensive and anticholinergic symptoms; rarely pigmentation and photosensitivity reactions rare; extrapyramidal symptoms are common, particularly acute dystonia and akathisia (especially in thyrotoxic patients); rarely weight loss, and hypoglycaemia, 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. Counselling 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 anti-depressants for maintenance treatment (see section 24.2.2). 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 less sedative effects include imipramine [not included on the 15th WHO Model List] . 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 overdosage is associated with a high rate of fatality.

Fluoxetine is a SSRI which 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

Tablet: 25 mg (hydrochloride).

Amitriptyline is a representative tricyclic antidepressant. Various medicines can serve as alternatives.

Uses: 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 2) and breastfeeding (Appendix 3); the elderly (reduce dose); hepatic impairment (Appendix 5); thyroid disease; phaeochromocytoma; history of mania or psychoses (may aggravate psychotic symptoms); angle-closure glaucoma, history of urinary retention; concurrent electroconvulsive therapy; avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension); **interactions:** Appendix 1.

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); behavioural disturbances; hypomania or mania, confusion or delirium (particularly in the elderly), headache, interference with sexual function, blood sugar changes; increased appetite and weight gain (occasional weight loss); endocrine adverse effects such as testicular enlargement, gynaecomastia and galactorrhoea; convulsions, movement disorders and dyskinesias, dysarthria, paraesthesia, taste disturbances, tinnitus, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (may be due to 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

Capsule or tablet: 20 mg (present as hydrochloride).

Uses: moderate to severe major depression.

Contraindications: 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 2) and breastfeeding (Appendix 3); hepatic impairment (Appendix 5); avoid abrupt withdrawal; children and adolescents (increased risk of suicide); **interactions:** Appendix 1.

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, 20–60 mg once daily (20–40 mg once daily in the elderly).

NOTE. Consider the long duration of action of fluoxetine when adjusting dosage.

Adverse effects: gastrointestinal disturbances, anorexia with weight loss, postural hypotension, pharyngitis, dyspnoea, 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, galactorrhoea, arthralgia, myalgia, visual disturbances, photosensitivity, chills, increased sweating, dry mouth, alopecia, rash (may be 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, hyponatraemia, 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, paraesthesia, sleep disturbances, fatigue, agitation, tremor, and sweating (particularly if withdrawn too abruptly).

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 (section 24.1) 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 1). 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 (section 24.2.1). 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/litre (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/litre, 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, haemodialysis 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

Tablet (scored): 100 mg; 200 mg.

Uses: prophylaxis of bipolar disorder unresponsive to or intolerant of lithium; epilepsy, trigeminal neuralgia (section 5).

Contraindications: atrioventricular conduction abnormalities; history of bone marrow depression; porphyria.

Precautions: hepatic impairment (Appendix 5); renal impairment (Appendix 4); cardiac disease (see also Contraindications above); skin reactions (see also Adverse effects below); history of blood disorders (monitor blood counts before and during treatment); glaucoma; pregnancy (risk of neural tube defects and neonatal bleeding; Appendix 2); breastfeeding (Appendix 3); avoid sudden withdrawal; **interactions:** Appendix 1.

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 which is severe, progressive and associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative).

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery or driving.

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: dizziness, drowsiness, headache, ataxia, blurred vision; diplopia (may be associated with high plasma concentrations); gastrointestinal intolerance including nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhoea, or constipation; commonly, mild transient generalized erythematous rash (withdraw if rash worsens or is accompanied by other symptoms); leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis, and aplastic anaemia); cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, and disturbances of bone metabolism with osteomalacia also reported; confusion and agitation in the elderly.

Lithium carbonate

Capsule or tablet: 300 mg.

Uses: treatment and prophylaxis of mania; prophylaxis of bipolar disorder and recurrent depression.

Contraindications: renal impairment (Appendix 4); cardiac insufficiency; conditions with sodium imbalance such as Addison disease.

Precautions: measure serum lithium concentration about 4 days after starting treatment, then weekly until stabilized, and then at least once every 3 months; monitor renal function and thyroid function every 6–12 months on stabilized regimens (risk of hypothyroidism; see also note on Patient advice below); maintain adequate fluid and sodium intake; reduce dose or discontinue in diarrhoea, vomiting, and intercurrent infection (especially if associated with profuse sweating); psoriasis (risk of exacerbation); pregnancy (Appendix 2) and breastfeeding (Appendix 3); the elderly (reduce dose); diuretic treatment, myasthenia gravis; surgery; avoid abrupt withdrawal (see also introductory note above); **interactions:** Appendix 1.

PATIENT ADVICE. Patients should maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake. Patients should be advised to seek medical attention if symptoms of hypothyroidism (for example, feeling cold, lethargy) develop (women are at greater risk).

NOTE. Different preparations vary widely in bioavailability; a change in the preparation used requires the same precautions as initiation of treatment.

Dose:

Treatment of mania (general guidelines only; see also note below), *by mouth*, **ADULT,** 0.6–1.8 g daily (300–900 mg daily in the elderly).

Prophylaxis of mania, bipolar disorder and recurrent depression (general guidelines only; see also note below), *by mouth*, **ADULT,** 0.6–1.2 g daily (300–900 mg daily in the elderly).

NOTE. Dosage of lithium depends on the preparation chosen since different preparations vary widely in bioavailability. Dosage should be adjusted to achieve a serum lithium concentration of 0.4–1 mmol/litre (aim for the lower end of the range for maintenance therapy and in the elderly) based on samples taken 12 hours after a dose; serum concentrations should be measured 4–7 days after starting treatment, then every week until dosage has remained unchanged for 4 weeks, and then every 3 months.

DOSAGE REGIMENS. For dose information for a specific preparation, consult manufacturer's literature.

Adverse effects: gastrointestinal disturbances, fine tremor, renal impairment (particularly impaired urinary concentration and polyuria), polydipsia, leukocytosis, weight gain and oedema (may respond to dose reduction); hyperparathyroidism and hypercalcaemia reported; signs of intoxication include blurred vision, muscle weakness, increasing gastrointestinal

disturbances (anorexia, vomiting, diarrhoea), increased central nervous system disturbances (mild drowsiness and sluggishness, increasing to giddiness with ataxia, coarse tremor, lack of co-ordination, and dysarthria) and require withdrawal of treatment; goitre, raised antidiuretic hormone concentration, hypothyroidism, hypokalaemia, ECG changes, and kidney changes also reported; with severe overdosage (serum concentrations above 2 mmol/litre), hyperreflexia and hyperextension of the limbs, convulsions, toxic psychoses, syncope, renal failure, circulatory failure, coma, and occasionally death.

Valproic acid

Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate).

Uses: acute mania; epilepsy (section 5).

Contraindications: active liver disease, family history of severe hepatic dysfunction; pancreatitis; porphyria.

Precautions: hepatic impairment (monitor liver function before and during therapy), especially in patients most at risk (those with metabolic disorders, degenerative disorders, organic brain disease, or severe seizure disorders associated with mental retardation) (Appendix 5); ensure no undue potential for bleeding before starting valproic acid, and before major surgery or anticoagulant therapy; renal impairment (Appendix 4); pregnancy (risk of neural tube defects and neonatal bleeding; Appendix 2); breastfeeding (Appendix 3); systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal; **interactions:** Appendix 1.

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 malaise, weakness, anorexia, lethargy, oedema, vomiting, abdominal pain, drowsiness, jaundice, or spontaneous bruising or bleeding develop.

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 diagnosed.

Dose:

Acute mania, *by mouth*, **ADULT,** initially 700 mg daily in divided doses, increased as quickly as possible to achieve the optimal response (maximum, 70 mg/kg daily but monitor patient closely if dose is greater than 52 mg/kg daily).

Adverse effects: gastrointestinal irritation, nausea, increased appetite and weight gain, hyperammonaemia; ataxia, tremor; transient hair loss (regrowth may be curly); oedema, thrombocytopenia, inhibition of platelet aggregation; impaired hepatic function and rarely fatal hepatic failure (withdraw

treatment immediately if malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, or drowsiness develop; see also note on Blood or hepatic disorders under Precautions above); sedation and also increased alertness reported; behavioural disturbances; rarely pancreatitis (measure plasma amylase if acute abdominal pain develops; see also note on Pancreatis under Precautions above); extrapyramidal symptoms; blood disorders including leukopenia, pancytopenia, red cell hypoplasia, and fibrinogen reduction; irregular menstrual periods, amenorrhoea, gynaecomastia, hearing loss, Fanconi syndrome, dementia, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme), vasculitis, hirsutism, and acne reported.

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.

Diazepam

Tablet (scored): 2 mg; 5 mg.

Drug subject to international control under the Convention on Psychotropic Substances (1971).

Diazepam is a representative benzodiazepine anxiolytic and hypnotic. Various medicines can serve as alternatives.

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 apnoea; severe hepatic impairment; myasthenia gravis.

Precautions: respiratory disease; muscle weakness; history of alcohol or drug abuse, marked personality disorder; pregnancy (Appendix 2) and breastfeeding (Appendix 3); elderly or debilitated (reduce dose); hepatic impairment (reduce dose but avoid if severe; Appendix 5), renal impairment (Appendix 4); avoid prolonged use and abrupt withdrawal; porphyria; **interactions:** Appendix 1.

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery or driving.

Dose:

Anxiety, *by mouth*, **ADULT,** 2 mg 3 times daily, increased if necessary to 15–30 mg daily in divided doses (reduced to half the adult dose in the elderly and debilitated patients).

Insomnia, *by mouth*, **ADULT,** 5–15 mg at bedtime.

Adverse effects: drowsiness and lightheadedness 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, behavioural and psychological treatments. Antidepressants such as **clomipramine,** which inhibit reuptake of serotonin, have been found to be effective.

Panic attacks may be treated with behavioural or cognitive therapy. If this management fails, drug therapy may be tried. Some tricyclic antidepressants including clomipramine, or some selective serotonin reuptake inhibitors (SSRIs) can reduce frequency of attacks or prevent them completely. Benzodiazepines (section 24.3) may be used in panic attacks resistant to antidepressants.

Clomipramine

Capsule: 10 mg; 25 mg (hydrochloride).

Uses: phobic and obsessional states; panic attacks.

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 2) and breastfeeding (Appendix 3); the elderly; hepatic impairment (Appendix 5); thyroid disease; phaeochromocytoma; history of mania, and psychoses (may aggravate psychotic symptoms); angle-closure glaucoma; history of urinary retention; concurrent electroconvulsive therapy; avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension); **interactions:** Appendix 1.

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.

Adverse effects: sedation, dry mouth, blurred vision (disturbance of accommodation, increased intraocular pressure), constipation, nausea, difficulty in micturition; cardiovascular adverse effects particularly with high dosage including ECG changes, arrhythmias, postural hypotension, tachycardia, and syncope; sweating, tremor, rash, hypersensitivity reactions (urticaria including photosensitivity); behavioural disturbances; hypomania or mania, confusion or delirium (particularly in the elderly), headache,

interference with sexual function, blood sugar changes; increased appetite and weight gain (occasional weight loss); endocrine adverse effects such as testicular enlargement, gynaecomastia, and galactorrhoea; convulsions, movement disorders and dyskinesias, dysarthria, paraesthesia, taste disturbances, tinnitus, fever, agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (may be due to inappropriate antidiuretic hormone secretion); abnormal liver function test, diarrhoea; hair loss reported.

24.5 Medicines used in substance-dependence programmes

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 programme. **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 [not included on the 15th WHO Model List] 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.

Methadone

Concentrate for oral liquid: 5 mg/ml; 10 mg/ml (hydrochloride).
Oral liquid: 5 mg/5 ml; 10 mg/5 ml.

Drug subject to international control under the Single Convention on Narcotic Drugs (1961).

Methadone is a representative opioid agonist for use in opioid dependence. Bupremorphine can serve as an alternative.

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.

Uses: 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 4); hepatic impairment (Appendix 5); risk of toxicity in children and non-dependant adults or if tolerance incorrectly assessed in dependent adults; severe withdrawal symptoms on abrupt withdrawal; hypothyroidism; convulsive disorders; decreased respiratory reserve and acute asthma; hypotension; prostatic hypertrophy; pregnancy (Appendix 2); breastfeeding (Appendix 3); overdosage (section 4.2), **interactions:** Appendix 1.

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 (maximum 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).

SECTION 25:
Medicines acting on the respiratory tract

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25.1 Antiasthmatics and medicines for chronic obstructive pulmonary disease

Asthma

Asthma is a chronic inflammatory disease characterized by episodes of reversible airways 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 (see tables on treatment options, pages 477-478).

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 candidosis. 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 beta$_2$-agonists, corticosteroids, leukotriene-receptor antagonists [not included on the 15th WHO Model List], and theophylline [not included on the 15th WHO Model List].

Parenteral

Drugs such as beta$_2$-agonists, corticosteroids, and aminophylline [not included on the 15th WHO Model List] 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 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.

Breastfeeding

Inhaled drugs, oral prednisolone and oral theophylline can be taken during breastfeeding.

Acute exacerbation of asthma

Severe asthma can be fatal and **must** be treated promptly and energetically. Acute severe asthma attacks require hospital admission where resuscitation facilities are immediately available.

Severe asthma is characterized by persistent dyspnoea (even at rest) that is poorly relieved by bronchodilators, exhaustion, a high pulse rate (usually more than 120/minute), 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 beta$_2$-agonist, **salbutamol** or terbutaline [not included on the 15th WHO Model List] 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 beta$_2$-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, maximum, 20 mg; 5–15 years, maximum, 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 beta$_2$-agonist; both cause more adverse effects than nebulized beta$_2$-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 beta$_2$-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.

TREATMENT OF CHRONIC ASTHMA: INFANTS AND YOUNG CHILDREN UNDER 5 YEARS

Preferred treatments in bold print

Steps	Long-term preventive (daily medications)	Quick relief
STEP 1 **Intermittent asthma**[a]	None needed in the majority of children; in exceptional cases (for example, active children who do not exercise to a planned schedule), regular long-term preventive medication may be needed	Short-acting **inhaled beta$_2$-agonist** as needed for symptoms Intensity of treatment will depend on severity of attack Inhaled beta$_2$-agonist *or* sodium cromoglicate *or* a leukotriene receptor antagonist before exercise *or* exposure to allergen
STEP 2 **Mild persistent asthma**	*Either* **inhaled corticosteroid**[b] (beclometasone, 50-200 micrograms twice daily) *or* a leukotriene receptor antagonist *or* modified-release theophylline *or* sodium cromoglicate	Short-acting **inhaled beta$_2$-agonist**[c] as needed for symptoms (not to exceed 3-4 times daily)
STEP 3 **Moderate persistent asthma**	**Inhaled corticosteroid** (beclometasone, 400-800 micrograms daily in divided doses) *plus* if needed *either* Long-acting bronchodilators (modified-release theophylline) *or* a leukotriene receptor antagonist *or* long-acting oral beta$_2$-agonist *or* High-dose **inhaled corticosteroid** (beclometasone, over 800 micrograms daily in divided doses)	Short-acting **inhaled beta$_2$-agonist**[d] as needed for symptoms (not to exceed 3-4 times daily)
STEP 4 **Severe persistent asthma**	High-dose **inhaled corticosteroid** (beclometasone, over 800 micrograms daily in divided doses) *plus* Long-acting **inhaled beta$_2$-agonist** twice daily *plus* if needed Modified-release theophylline[e] *or* a leukotriene receptor antagonist[e] *or* long-acting oral beta$_2$-agonist[e] *or* oral corticosteroid in the lowest dose possible, best given as a single morning dose (use soluble tablets if necessary for younger children)	Short-acting **inhaled beta$_2$-agonist**[f] as needed for symptoms (not to exceed 3-4 times daily)
STEP UP	If control of asthma is not achieved or is lost, consider stepping up treatment, however, first review patient medication technique and compliance.	
STEP DOWN	If control of asthma is maintained for at least 3 months, gradually decrease maintenance treatment to determine the minimum level of treatment required.	
NOTE: Inhaled corticosteroids given through metered-dose inhalers should be administered with large-volume spacer devices (an face-mask if appropriate); inhaled broncholidators given through metered-dose inhalers may also be administered with large-volume spacer devices if necessary. If patient is unable to take inhaled drugs even with large-volume spacer devices and face-mask if appropriate, then consider administration via a nebulizer.		

a Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma

b Alternative to inhaled corticosteroids less effective

c Alternatives to short-acting inhaled beta$_2$-agonist are inhaled ipratropium, short-acting oral beta$_2$-agonist and short-acting theophylline; these alternatives have slower onset of action or higher risk of side-effects

d Alternatives to short-acting inhaled beta$_2$-agonist are inhaled ipratropium, short-acting oral beta$_2$-agonist and short-acting theophylline; these alternatives have slower onset of action or higher risk of side-effects

e Also can be used as alternative to long-acting inhaled beta$_2$-agonist if necessary (although long-acting inhaled beta$_2$-agonist is preferred)

f Alternatives to short-acting inhaled beta$_2$-agonist are inhaled ipratropium, short-acting oral beta$_2$-agonist and short-acting theophylline; these alternatives have slower onset of action or higher risk of side-effects

TREATMENT OF CHRONIC ASTHMA: ADULTS AND CHILDREN OVER 5 YEARS

Preferred treatments in bold print

Steps	Long-term preventive (daily medications)	Quick relief
STEP 1 **Intermittent asthma**[a]	None needed.	Short-acting **inhaled beta$_2$-agonist** as needed for symptoms Intensity of treatment will depend on severity of attack Inhaled beta$_2$-agonist *or* sodium cromoglicate *or* a leukotriene receptor antagonist before exercise *or* exposure to allergen
STEP 2 **Mild persistent asthma**	*Either* **inhaled corticosteroid**[b] (beclometasone, 100-250 micrograms twice daily) *or* sodium cromoglicate *or* modified-release theophylline *or* a leukotriene receptor antagonist	Short-acting **inhaled beta$_2$-agonist**[c] as needed for symptoms (not to exceed 3-4 times daily)
STEP 3 **Moderate persistent asthma**	**Inhaled corticosteroid** (beclometasone, 100-500 micrograms twice daily) *plus* if needed *either* Long-acting bronchodilators (**long-acting inhaled beta$_2$-agonist** *or* modified-release theophylline) *or* a leukotriene receptor antagonist *or* long-acting oral beta$_2$-agonist *or* High-dose **inhaled corticosteroid** (beclometasone, over 1 mg daily in divided doses)	Short-acting **inhaled beta$_2$-agonist**[d] as needed for symptoms (not to exceed 3-4 times daily)
STEP 4 **Severe persistent asthma**	High-dose **inhaled corticosteroid** (beclometasone, over 1 mg daily in divided doses) *plus* Long-acting **inhaled beta$_2$-agonist** twice daily *plus* if needed Modified-release theophylline[e] *or* a leukotriene receptor antagonist[e] *or* long-acting oral beta$_2$-agonist[e] *or* oral corticosteroid in the lowest dose possible, best given as a single morning dose (use soluble tablets if necessary for younger children)	Short-acting **inhaled beta$_2$-agonist**[f] as needed for symptoms (not to exceed 3-4 times daily)
STEP UP	If control of asthma is not achieved or is lost, consider stepping up treatment, however, first review patient medication technique and compliance.	
STEP DOWN	If control of asthma is maintained for at least 3 months, gradually decrease maintenance treatment to determine the minimum level of treatment required.	
NOTE: Inhaled corticosteroids given through metered-dose inhalers should be administered with large-volume spacer devices (an face-mask if appropriate); inhaled broncholidators given through metered-dose inhalers may also be administered with large-volume spacer devices if necessary. If patient is unable to take inhaled drugs even with large-volume spacer devices and face-mask if appropriate, then consider administration via a nebulizer.		

a Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma
b Alternative to inhaled corticosteroids less effective
c Alternatives to short-acting inhaled beta$_2$-agonist are inhaled ipratropium, short-acting oral beta$_2$-agonist and short-acting theophylline; these alternatives have slower onset of action or higher risk of side-effects
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e Also can be used as alternative to long-acting inhaled beta$_2$-agonist if necessary (although long-acting inhaled beta$_2$-agonist is preferred)
f Alternatives to short-acting inhaled beta$_2$-agonist are inhaled ipratropium, short-acting oral beta$_2$-agonist and short-acting theophylline; these alternatives have slower onset of action or higher risk of side-effects

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 chronic obstructive pulmonary disease and may be prevented by vaccination, for example, with the influenza vaccine (section 19.3).

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 beta$_2$-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 beta$_2$-adrenoceptor agonist, for example, salmeterol [not included on the 15th WHO Model List] 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 beta$_2$-adrenoceptor agonist; if no benefit is seen after 4 weeks, treatment should be discontinued. Exacerbations of chronic obstructive pulmonary disease 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 chronic obstructive pulmonary disease and hypoxaemia.

Beta$_2$-adrenoceptor agonists (beta$_2$-adrenoceptor stimulants)

The adrenoreceptors in the bronchi are mainly of the beta$_2$ type, and their stimulation causes bronchial muscles to relax. The beta$_2$-adrenoceptor agonists (stimulants) include salbutamol, terbutaline, and fenoterol.

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 (see tables on treatement of chronic asthma) 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. Hypokalaemia may also result from beta$_2$-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 diarrhoea and when plasma concentrations exceed the recommended range of 10–20 mg/litre (55–110 micromol/litre) 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 chronic obstructive pulmonary disease.

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 beta$_2$-adrenoceptor agonist more than once a week over a 3-month period and some episodes 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 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 candidosis, dysphonia, and occasional coughing from upper airway irritation. The use of spacing devices reduces oropharyngeal deposition and thus reduces

the incidence of candidosis; 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 beta$_2$-agonist before using a corticosteroid inhaler. The risk for systemic effects of inhaled corticosteroids is small and is dependent upon 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 (see also section 18.1).

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 which controls symptoms.

Sodium cromoglicate

Sodium cromoglicate [not included on the 15th WHO Model List] 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 beta$_2$-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 chronic obstructive pulmonary disease.

Leukotriene receptor antagonists

The leukotriene receptor antagonists [not included on the 15th WHO Model List], including montelukast, pranlukast, and zafirlukast, 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.

Beclometasone

Inhalation (aerosol): 50 micrograms per dose (dipropionate); 250 micrograms (dipropionate) per dose.

Beclometasone dipropionate is a representative corticosteroid. Various medicines can serve as alternatives.

Uses: chronic asthma not controlled by short-acting beta$_2$-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; **interactions:** Appendix 1.

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 candidosis, 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 beta$_2$-adrenoceptor agonist or by transfer

from aerosol to powder inhalation); rarely urticaria, rash, and angioedema; very rarely anxiety, sleep disorders, and behavioural changes.

CANDIDOSIS. Candidosis 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 candidosis.

Epinephrine (adrenaline)

Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.

See section 3.

Ipratropium bromide

Inhalation (aerosol): 20 micrograms/metered dose.

Uses: chronic asthma; chronic obstructive pulmonary disease.

Precautions: prostatic hypertrophy; glaucoma (standard doses unlikely to be harmful but reported with nebulized drug, particularly in association with nebulized salbutamol; care needed to protect patient's eyes from drug powder or nebulized drug); medical supervision necessary for first dose of nebulized solution (risk of paradoxical bronchospasm).

Dose:

Chronic asthma, chronic obstructive pulmonary disease, *by aerosol inhalation*, **ADULT,** 20–40 micrograms, 3–4 times daily; **CHILD** up to 6 years, 20 micrograms 3 times daily; **CHILD** 6–12 years, 20–40 micrograms 3 times daily.

Chronic obstructive pulmonary disease, *by inhalation of nebulized solution*, **ADULT,** 250–500 micrograms 3–4 times daily.

Adjunct in acute bronchospasm, *by inhalation of nebulized solution*, **ADULT,** 500 micrograms repeated as required; **CHILD** up to 6 years, 125–250 micrograms; maximum, 1 mg daily; **CHILD** 6–12 years, 250 micrograms; maximum, 1 mg daily.

Adverse effects: occasionally dry mouth; rarely urinary retention and constipation; tachycardia and atrial fibrillation also reported.

Salbutamol

Inhalation (aerosol): 100 micrograms (as sulfate) per dose.
Injection: 50 micrograms (as sulfate)/ml in 5-ml ampoule.
Oral liquid: 2 mg/5 ml.
Respirator solution for use in nebulizers: 5 mg (as sulfate)/ml.
Tablet: 2 mg; 4 mg (as sulfate).

Salbutamol is a representative beta$_2$-adrenoceptor agonist. Various drugs can serve as alternatives.

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 2); breastfeeding (Appendix 3); diabetes mellitus, especially intravenous administration (ketoacidosis reported; monitor blood glucose); **interactions:** Appendix 1.

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; *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 hypoxaemia may occur—consider oxygen supplementation).

Adverse effects: hypokalaemia after high doses (see introductory note above); arrhythmias, tachycardia, palpitations, fine tremor (usually hands), muscle cramps, headache, insomnia, behavioural disturbances in children; paradoxical bronchospasm, urticaria, and angioedema also reported; slight pain on intramuscular injection.

25.2 Other medicines acting on the respiratory tract

Caffeine citrate

Injection: 20 mg/ml (equivalent to 10 mg caffeine base/ml).
Oral liquid: 20 mg/ml (equivalent to 10 mg caffeine base/ml).

Caffeine citrate, a respiratory stimulant, is used for neonatal apnoea in preterm infants (those born at less than 35 weeks gestational age and weighing under 2 kg). It is preferred over other xanthines such as theophylline (section 25.1), as caffeine citrate has a better safety profile and does not require routine medicine level monitoring. Other causes of neonatal apnoea should be sought and treated before treatment with caffeine citrate is started (e.g. sepsis, hypothermia, hypoglycaemia, hypoxaemia, anaemia, seizures).

Uses: neonatal apnoea in preterm infants.

Precautions: cardiovascular disorders; renal impairment (Appendix 4); hepatic impairment (Appendix 5).

Dose:

NOTE. All doses expressed as caffeine citrate.

Neonatal apnoea, *by mouth* or *by intravenous injection*, **NEONATE,** 20 mg/kg as a loading dose, then 5 mg/kg once daily starting 24 hours after loading dose; continue for 4–5 days after cessation of apnoea.

NOTE. Caffeine citrate, 2 mg = caffeine base, 1 mg.

Adverse effects: lethargy (physical sign of withdrawal); feeding intolerance; irritability, excessive central nervous system stimulation, tachycardia (early sign of toxicity), hyperglycaemia or hypoglycaemia; rarely acidosis, disseminated intravascular coagulation, haemorrhage, lung oedema, gastritis, renal failure, retinopathy of prematurity, and sepsis.

SECTION 26:
Solutions correcting water, electrolyte and acid–base disturbances

26.1 Oral 487

26.2 Parenteral 488

26.3 Miscellaneous 493

26.1 Oral

Oral rehydration salts

See Section 17.5.1.

Potassium chloride

Powder for solution.

Compensation for potassium loss is necessary in patients taking digoxin (sections 12.2 and 12.4) or other antiarrhythmic 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 faeces (chronic diarrhoea 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 hypokalaemia due to diuretics such as furosemide or the thiazides when these are given to eliminate oedema (see section 16).

For the prevention of hypokalaemia, 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 hyperkalaemia.

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 hypokalaemia; electrolyte imbalance (section 26.2).

Contraindications: severe renal impairment; plasma potassium concentration above 5 mmol/litre.

Precautions: the elderly, mild to moderate renal impairment (close monitoring required, Appendix 4); history of peptic ulcer; **interactions**: Appendix 1.

IMPORTANT. Extra caution is required when given with drugs liable to raise plasma potassium concentrations, such as potassium-sparing diuretics, ACE inhibitors or ciclosporin.

Dose:

Prevention of hypokalaemia, *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

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 is otherwise unable to take adequate amounts by mouth.

The nature and severity of the electrolyte imbalance must be assessed from 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 litres, 2–3 litres 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 hyponatraemia 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/litre in 24 hours. In severe hyponatraemia, 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 which 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 diarrhoea 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 litres daily and 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 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 hypercalcaemia. 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 litres.

Glucose solutions are also given in regimens with calcium, bicarbonate, and insulin for the emergency treatment of *hyperkalaemia*. They are also given, after correction of hyperglycaemia, during treatment of *diabetic ketoacidosis*, when they must be accompanied by continuing insulin infusion (see also section 18.5).

If glucose or sugar cannot be given orally to treat *hypoglycaemia*, glucose, 50% may be given intravenously into a large vein through 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 litres (4 litres of sodium chloride and 2 litres 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 *hyperkalaemia*.

Intravenous **potassium chloride** in sodium chloride solution is the initial treatment for the correction of *severe hypokalaemia* 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 hyperkalaemia 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

Injectable solution: 5%; 10% isotonic; 50% hypertonic.

Uses: fluid replacement without significant electrolyte deficit; treatment of hypoglycaemia.

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 hypoglycaemia, *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; oedema or water intoxication (on prolonged administration or rapid infusion of large volumes of isotonic solutions); hyperglycaemia (on prolonged administration of hypertonic solutions).

Glucose with sodium chloride

Injectable solution: 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/l, Cl-30 mmol/l).

Uses: fluid and electrolyte replacement.

Precautions: restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary oedema, and toxaemia 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 oedema.

Potassium chloride

Solution: 11.2% in 20-ml ampoule (equivalent to K^+ 1.5 mmol/ml, Cl- 1.5 mmol/ml).

Uses: electrolyte imbalance; prevention and treatment of hypokalaemia (section 26.1).

Precautions: for intravenous infusion the concentration of solution should not usually exceed 3.2 g (43 mmol)/litre; administer under specialist advice and with plasma potassium and ECG monitoring; renal impairment (Appendix 4); **interactions:** Appendix 1.

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.

Sodium chloride

Injectable solution: 0.9% isotonic (equivalent to Na^+ 154 mmol/l, Cl- 154 mmol/l).

Uses: electrolyte and fluid replacement.

Precautions: restrict intake in impaired renal function (Appendix 4), cardiac failure, hypertension, peripheral and pulmonary oedema, and toxaemia 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 oedema.

Sodium hydrogen carbonate

Injectable solution: 1.4% isotonic (equivalent to Na^+ 167 mmol/l, HCO_3-167 mmol/l).
Solution: 8.4% in 10-ml ampoule (equivalent to Na^+ 1000 mmol/l, HCO_3-1000 mmol/l).

Uses: metabolic acidosis.

Contraindications: metabolic or respiratory alkalosis, hypocalcaemia, hypochlorhydria.

Precautions: restrict intake in impaired renal function (Appendix 4), cardiac failure, hypertension, peripheral and pulmonary oedema, and toxaemia during pregnancy; monitor electrolytes and acid–base status; **interactions:** Appendix 1.

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 hypokalaemia and metabolic alkalosis, especially in renal impairment; large doses may give rise to sodium accumulation and oedema.

Sodium lactate, compound solution

Injectable solution.

Compound solution of sodium lactate is a representative intravenous electrolyte solution. Various solutions can serve as alternatives.

Uses: pre- and perioperative fluid and electrolyte replacement; hypovolaemic shock.

Contraindications: metabolic or respiratory alkalosis; hypocalcaemia or hypochlorhydria.

Precautions: restrict intake in impaired renal function (Appendix 4), cardiac failure, hypertension, peripheral and pulmonary oedema, and toxaemia during pregnancy; **interactions:** Appendix 1.

Dose:

Fluid and electrolyte replacement or hypovolaemic shock, *by intravenous infusion*, **ADULT** and **CHILD,** determined on the basis of clinical and, whenever possible, electrolyte monitoring (see also introductory note above).

Adverse effects: excessive administration may cause metabolic alkalosis; administration of large doses may give rise to oedema.

26.3 Miscellaneous

Water for injection

2-ml; 5-ml; 10-ml ampoules.

Uses: in preparations intended for parenteral administration and in other sterile preparations.

SECTION 27:
Vitamins and minerals

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 subclinical 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 D_2), and pyridoxine (vitamin B_6) 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 diarrhoea. Universal vitamin A distribution involves the periodic administration of supplemental doses to all preschool-age children, with priority given to the age group, 6 months–3 years, or regions at greatest risk of clinical and subclinical 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 child-bearing age. Vitamin 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 child-bearing 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 (i.e. as for 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 B_1) 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 oedema. 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 B_2) 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 B_6) 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 anaemia. 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 hyperlipidaemias. 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 B_{12} used to treat vitamin B_{12} 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 B_{12} is associated with megaloblastic anaemia. Folic acid should not be used in undiagnosed megaloblastic anaemia unless vitamin B_{12} is administered concurrently, otherwise neuropathy may be precipitated (see section 10.1). Supplementation with folic acid, 400 micrograms daily, is recommended for women of child-bearing 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 D_2) and colecalciferol (vitamin D_3). 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 D_3) 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 D_3 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 D_3. Vitamin D is also used in deficiency states caused by intestinal

malabsorption or chronic liver disease and for the hypocalcaemia that is associated with hypoparathyroidism.

Phytomenadione (vitamin K) that 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 anaemia see section 10.1.

Ascorbic acid

Tablet: 50 mg.

Also known as vitamin C.

Uses: prevention and treatment of scurvy.

Dose:

Prophylaxis of scurvy, *by mouth*, **ADULT** and **CHILD,** 25–75 mg daily.

Treatment of scurvy, *by mouth*, **ADULT** and **CHILD,** not less than 250 mg daily in divided doses.

Adverse effects: gastrointestinal disturbances reported with large doses.

Calcium gluconate

Injection: 100 mg/ml in 10-ml ampoule.

Calcium gluconate is a complementary list medicine.

Calcium supplements, in the form of calcium gluconate, are usually only required where 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 which is double the recommended daily amount reduces the rate of bone loss. In hypocalcaemic tetany, calcium gluconate must be given parenterally but plasma calcium must be monitored. Calcium gluconate is also used in cardiac resuscitation.

Uses: hypocalcaemic tetany.

Contraindications: conditions associated with hypercalcaemia and hypercalciuria (for example, some forms of malignant disease).

Precautions: monitor plasma calcium concentration; renal impairment (Appendix 4); sarcoidosis; history of nephrolithiasis; **interactions**: Appendix 1.

Dose:

Hypocalcaemic 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.

Ergocalciferol

Capsule or tablet: 1.25 mg (50 000 IU).
Oral liquid: 250 micrograms/ml (10 000 IU/ml).

Also known as vitamin D_2.

Ergocalciferol is a representative vitamin D compound. Various vitamin D compounds can serve as alternatives.

NOTE. If there is no plain vitamin D tablet available for the treatment of simple deficiency, combined calcium and ergocalciferol tablets may be used but the calcium is unnecessary.

Uses: prevention and treatment of simple vitamin D deficiency; treatment of vitamin D deficiency caused by malabsorption or chronic liver disease; hypocalcaemia associated with hypoparathyroidism.

Contraindications: hypercalcaemia; metastatic calcification.

Precautions: ensure correct dose in infants; monitor plasma calcium at weekly intervals in patients receiving high doses or those with renal impairment; nausea and vomiting may indicate overdose and hypercalcaemia; pregnancy (Appendix 2) and breastfeeding (Appendix 3); **interactions:** Appendix 1.

Dose:

Prevention of vitamin D deficiency, *by mouth*, **ADULT** and **CHILD,** 10 micrograms (400 IU) daily.

Treatment of vitamin D deficiency, *by mouth*, **ADULT,** 1.25 mg (50 000 IU) daily for a limited period; **CHILD,** 75–125 micrograms (3000–5000 IU) daily.

Hypocalcaemia associated with hypoparathyroidism, *by mouth*, **ADULT,** 2.5 mg (100 000 IU) daily; **CHILD,** up to 1.5 mg (60 000 IU) daily.

Adverse effects: symptoms of overdosage include anorexia, lassitude, nausea and vomiting, diarrhoea, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine; tissue calcification may occur if dose of 1.25 mg continued for several months.

Iodine

Capsule: 200 mg.
Iodized oil: 1 ml (480 mg iodine); 0.5 ml (240 mg iodine) in ampoule (oral or injectable); 0.57 ml (308 mg iodine) in dispenser bottle.

NOTE. Iodized oil may also be given by mouth.

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 goitre 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 goitre 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.

Uses: prevention and treatment of iodine deficiency.

Contraindications: breastfeeding (Appendix 3).

Precautions: those over 45 years old or with nodular goitre (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 and Appendix 2).

Dose:

Endemic moderate to severe iodine deficiency, *by intramuscular injection*, **ADULT** woman of child-bearing age (including any stage of pregnancy), 480 mg once each year; *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 child-bearing 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; goitre and hypothyroidism; hyperthyroidism.

Nicotinamide

Tablet: 50 mg.

Nicotinamide is a representative vitamin B substance. Various compounds can serve as alternatives.

Uses: treatment of pellagra.

Dose:

Treatment of pellagra, *by mouth*, **ADULT,** up to 500 mg daily in divided doses.

Pyridoxine

Tablet: 25 mg (hydrochloride).

Also known as Vitamin B_6.

Uses: treatment of pyridoxine deficiency due to metabolic disorders; isoniazid neuropathy; sideroblastic anaemia.

Precautions: interactions: Appendix 1.

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 anaemia, *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

Capsule: 50 000 IU; 100 000 IU; 200 000 IU (as palmitate).
Oral oily solution: 100 000 IU (as palmitate)/ml in multidose dispenser.
Tablet (sugar-coated): 10 000 IU (as palmitate).
Water-miscible injection: 100 000 IU (as palmitate) in 2-ml ampoule.

Uses: prevention and treatment of vitamin A deficiency; prevention of complications of measles.

Precautions: pregnancy (teratogenic; see also introductory note above and Appendix 2) and breastfeeding (Appendix 3).

Dose:

Prevention of vitamin A deficiency (universal or targeted distribution programmes), *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 child-bearing 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 child-bearing age) and **CHILD** over 1 year, 200 000 IU on diagnosis, repeated the next day and again after 2 weeks; **ADULT** (woman of child-bearing age with severe signs of xerophthalmia) as for other adults; **ADULT** woman of child-bearing age with less severe symptoms, for example, night blindness, either 5000–10 000 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.

Riboflavin

Tablet: 5 mg.

Also known as Vitamin B_2.

Uses: vitamin B_2 deficiency.

Dose:

Treatment of vitamin B_2 deficiency, *by mouth*, **ADULT** and **CHILD,** up to 30 mg daily in divided doses.

Prophylaxis of vitamin B_2 deficiency, *by mouth*, **ADULT** and **CHILD,** 1–2 mg daily.

Sodium fluoride

In any appropriate topical formulation.

NOTE. Sodium fluoride may be used in any appropriate topical formulation.

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/litre, 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.

Uses: prevention of dental caries.

Contraindications: 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.

Thiamine

Tablet: 50 mg (hydrochloride).

Also known as Vitamin B_1.

Uses: prevention and treatment of vitamin B_1 deficiency.

Precautions: parenteral administration (see note above); breastfeeding (Appendix 3).

Dose:

Mild chronic thiamine deficiency, *by mouth*, **ADULT,** 10–25 mg daily.

Appendix 1: 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 which have similar or antagonistic pharmacological effects or adverse effects. They are usually predictable from a 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 which 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 which 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 only taken with caution and appropriate monitoring. Interactions with no symbol do not usually have serious consequences.

Abacavir		
	Methadone	Plasma concentration of methadone possibly reduced
	Phenobarbital	Plasma concentration of abacavir possibly reduced
	Phenytoin	Plasma concentration of abacavir possibly reduced
	Rifampicin	Plasma concentration of abacavir possibly reduced
Acetazolamide		
	Acetylsalicylic acid	Increased risk of toxicity when given with high-dose acetylsalicylic acid
	Alcohol	Enhanced hypotensive effect
	Amitriptyline	Increased risk of postural hypotension
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
*	Carbamazepine	Increased risk of hyponatraemia; acetazolamide increases plasma carbamazepine concentration
	Chlorpromazine	Enhanced hypotensive effect
	Cisplatin	Increased risk of nephrotoxicity and ototoxicity
	Clomipramine	Increased risk of postural hypotension
	Contraceptives, Oral	Antagonism of diuretic effect by estrogens
	Dexamethasone	Increased risk of hypokalaemia; antagonism of diuretic effect
	Diazepam	Enhanced hypotensive effect
*	Digoxin	Hypokalaemia caused by acetazolamide increases cardiac toxicity of digoxin
*	Enalapril	Enhanced hypotensive effect
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Increased risk of hypokalaemia
	Glyceryl trinitrate	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Increased risk of hypokalaemia
	Hydrocortisone	Increased risk of hypokalaemia; antagonism of diuretic effect
	Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
*	Lidocaine	Hypokalaemia caused by acetazolamide antagonizes action of lidocaine (interaction less likely when lidocaine is used topically)
*	Lithium	Excretion of lithium increased
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
	Phenobarbital	Increased risk of osteomalacia
	Phenytoin	Increased risk of osteomalacia
	Prednisolone	Increased risk of hypokalaemia; antagonism of diuretic effect
	Propranolol	Enhanced hypotensive effect
*	Quinidine	Cardiac toxicity of quinidine increased if hypokalaemia occurs; acetazolamide possibly reduces excretion of quinidine (increased plasma concentration)
	Salbutamol	Increased risk of hypokalaemia with high doses of salbutamol

	Sodium nitroprusside	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect
Acetylsalicylic acid		
	Acetazolamide	Increased risk of toxicity when given with high-dose acetylsalicylic acid
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Excretion of acetylsalicylic acid increased by alkaline urine
	Dexamethasone	Increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma salicylate concentration
	Enalapril	Antagonism of hypotensive effect; risk of renal impairment when acetylsalicylic acid given in doses of over 300 mg daily
*	Fluoxetine	Increased risk of bleeding
*	Heparin	Enhanced anticoagulant effect of heparin
	Hydrocortisone	Increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma salicylate concentration
*	Ibuprofen	Avoid concomitant use (increased adverse effects); antiplatelet effect of acetylsalicylic acid possibly reduced
*	Methotrexate	Reduced excretion of methotrexate (increased toxicity)
	Metoclopramide	Enhanced effect of acetylsalicylic acid (increased rate of absorption)
	Mifepristone	Manufacturer of mifepristone advises avoid concomitant use
	Phenytoin	Enhancement of effect of phenytoin
	Prednisolone	Increased risk of gastrointestinal bleeding and ulceration; prednisolone reduces plasma salicylate concentration
	Spironolactone	Antagonism of diuretic effect
	Valproic acid	Enhancement of effect of valproic acid
*	Warfarin	Increased risk of bleeding due to antiplatelet effect
Aciclovir		
	Ciclosporin	Increased risk of nephrotoxicity
Albendazole		
	Dexamethasone	Plasma albendazole concentration possibly increased
	Praziquantel	Increased plasma concentration of active metabolite of albendazole
Alcohol		
	Acetazolamide	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
*	Amitriptyline	Enhanced sedative effect
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Carbamazepine	Possibly enhanced CNS adverse effects of carbamazepine
	Chlorphenamine	Enhanced sedative effect
	Chlorpromazine	Enhanced sedative effect
*	Clomipramine	Enhanced sedative effect
	Codeine	Enhanced sedative and hypotensive effect
*	Cycloserine	Increased risk of convulsions
	Diazepam	Enhanced sedative effect
	Enalapril	Enhanced hypotensive effect
	Fluoxetine	Possibly enhanced sedative effect

	Fluphenazine	Enhanced sedative effect
	Furosemide	Enhanced hypotensive effect
	Glibenclamide	Enhanced hypoglycaemic effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Griseofulvin	Possibly enhanced effects of alcohol
	Haloperidol	Enhanced sedative effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Insulins	Enhanced hypoglycaemic effect
	Isosorbide dinitrate	Enhanced hypotensive effect
	Levamisole	Possibility of disulfiram-like reaction
	Metformin	Enhanced hypoglycaemic effect; increased risk of lactic acidosis
	Methadone	Enhanced hypotensive and sedative effects
	Methyldopa	Enhanced hypotensive effect
	Metronidazole	Disulfiram-like reaction
	Morphine	Enhanced sedative and hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Phenobarbital	Enhanced sedative effect
	Phenytoin	Plasma phenytoin concentration reduced with regular large amounts of alcohol
	Procarbazine	Disulfiram-like reaction
	Promethazine	Enhanced sedative effect
	Propranolol	Enhanced hypotensive effect
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect; plasma concentration of alcohol possibly increased by verapamil
*	Warfarin	Enhanced anticoagulant effect with large amounts of alcohol; major changes in alcohol consumption may affect anticoagulant control
Alcuronium		
*	Amikacin	Enhanced effects of alcuronium
	Carbamazepine	Antagonism of muscle relaxant effect (recovery from neuromuscular blockade accelerated)
*	Clindamycin	Enhanced muscle relaxant effect
*	Gentamicin	Enhanced muscle relaxant effect
	Halothane	Effects of alcuronium enhanced
	Lithium	Enhanced muscle relaxant effect
	Magnesium (parenteral)	Enhanced muscle relaxant effect
	Neostigmine	Antagonism of muscle relaxant effect
	Nifedipine	Enhanced muscle relaxant effect
	Phenytoin	Antagonism of muscle relaxant effect (accelerated recovery from neuromuscular blockade)
*	Procainamide	Enhanced muscle relaxant effect
	Propranolol	Enhanced muscle relaxant effect
	Pyridostigmine	Antagonism of muscle relaxant effect
*	Quinidine	Enhanced muscle relaxant effect
*	Streptomycin	Enhanced muscle relaxant effect
	Verapamil	Enhanced muscle relaxant effect
Allopurinol		
	Amoxicillin	Increased risk of rash

	Ampicillin	Increased risk of rash
*	Azathioprine	Effects of azathioprine enhanced and toxicity increased; reduce dose of azathioprine
	Ciclosporin	Plasma ciclosporin concentration possibly increased (risk of nephrotoxicity)
	Didanosine	Possibly increased plasma concentration of didanosine
	Hydrochlorothiazide	Increased risk of hypersensitivity, especially in renal impairment
*	Mercaptopurine	Effects of mercaptopurine enhanced and toxicity increased; reduce dose of mercaptopurine
	Warfarin	Anticoagulant effect possibly enhanced
Aluminium hydroxide		
	see Antacids	
Amikacin		
*	Alcuronium	Enhanced effects of alcuronium
	Amphotericin B	Increased risk of nephrotoxicity
	Capreomycin	Increased risk of nephrotoxicity and ototoxicity
*	Ciclosporin	Increased risk of nephrotoxicity
*	Cisplatin	Increased risk of nephrotoxicity and possibly of ototoxicity
*	Furosemide	Increased risk of ototoxicity
*	Neostigmine	Antagonism of effects of neostigmine
*	Pyridostigmine	Antagonism of effects of pyridostigmine
*	Suxamethonium	Enhanced effects of suxamethonium
	Vancomycin	Increased risk of nephrotoxicity and ototoxicity
*	Vecuronium	Enhanced effects of vecuronium
Amiloride		
	Alcohol	Enhanced hypotensive effect
	Amitriptyline	Increased risk of postural hypotension
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Carbamazepine	Increased risk of hyponatraemia
	Chlorpromazine	Enhanced hypotensive effect
*	Ciclosporin	Increased risk of hyperkalaemia
	Cisplatin	Increased risk of nephrotoxicity and ototoxicity
	Clomipramine	Increased risk of postural hypotension
	Contraceptives, Oral	Antagonism of diuretic effect by estrogens
	Dexamethasone	Antagonism of diuretic effect
	Diazepam	Enhanced hypotensive effect
*	Enalapril	Enhanced hypotensive effect; increased risk of severe hyperkalaemia
	Fluphenazine	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of diuretic effect
	Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
*	Lithium	Reduced lithium excretion (increased plasma lithium concentration and risk of toxicity)
	Methyldopa	Enhanced hypotensive effect

	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
*	Potassium salts	Increased risk of hyperkalaemia
	Prednisolone	Antagonism of diuretic effect
	Propranolol	Enhanced hypotensive effect
	Sodium nitroprusside	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect
Amitriptyline		
	Acetazolamide	Increased risk of postural hypotension
*	Alcohol	Enhanced sedative effect
	Amiloride	Increased risk of postural hypotension
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Atropine	Increased antimuscarinic adverse effects
	Biperiden	Increased antimuscarinic adverse effects
*	Carbamazepine	Antagonism of anticonvulsant effect (convulsive threshold lowered); accelerated metabolism of amitriptyline (reduced plasma concentration; reduced antidepressant effect)
	Chlorphenamine	Increased antimuscarinic and sedative effects
*	Chlorpromazine	Increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
	Codeine	Possibly enhanced sedative effect
	Contraceptives, Oral	Antagonism of antidepressant effect by estrogens but adverse effects of amitriptyline possibly increased due to increased plasma concentration of amitriptyline
	Diazepam	Enhanced sedative effect
*	Epinephrine	Increased risk of hypertension and arrhythmias (but local anaesthetics which contain epinephrine appear to be safe)
*	Ethosuximide	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Fluphenazine	Increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
	Furosemide	Increased risk of postural hypotension
	Glyceryl trinitrate	Reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under tongue owing to dry mouth)
*	Haloperidol	Increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
	Halothane	Increased risk of arrhythmias and hypotension
	Hydrochlorothiazide	Increased risk of postural hypotension
	Isoniazid	Increased plasma concentration of isoniazid
	Isosorbide dinitrate	Reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under tongue owing to dry mouth)
	Ketamine	Increased risk of arrhythmias and hypotension
	Levothyroxine	Enhanced effects of amitriptyline
	Lithium	Risk of toxicity
	Methadone	Sedative effects possibly increased
	Morphine	Possibly increased sedation
	Nitrous oxide	Increased risk of arrhythmias and hypotension

*	Phenobarbital	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of amitriptyline possibly accelerated (reduced plasma concentration)
*	Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered); possibly reduced plasma amitriptyline concentration
*	Procainamide	Increased risk of ventricular arrhythmias
	Promethazine	Increased antimuscarinic and sedative effects
*	Quinidine	Increased risk of ventricular arrhythmias
	Rifampicin	Plasma concentration of amitriptyline possibly reduced
*	Ritonavir	Plasma concentration possibly increased by ritonavir
	Spironolactone	Increased risk of postural hypotension
	Thiopental	Increased risk of arrhythmias and hypotension
*	Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Verapamil	Possibly increased plasma concentration of amitriptyline
*	Warfarin	Enhanced or reduced anticoagulant effect
Amlodipine		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Carbamazepine	Probably reduced effect of amlodipine
	Chlorpromazine	Enhanced hypotensive effect
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect
	Enalapril	Enhanced hypotensive effect
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Haloperidol	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of hypotensive effect
	Ibuprofen	Antagonism of hypotensive effect
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
	Mefloquine	Possible increased risk of bradycardia
	Methyldopa	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
*	Phenobarbital	Probably reduced effect of amlodipine
	Phenytoin	Probably reduced effect of amlodipine
	Prednisolone	Antagonism of hypotensive effect
	Propranolol	Enhanced hypotensive effect
*	Ritonavir	Possibly increased plasma concentration of amlodipine
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect

Amodiaquine		
	Chlorpromazine	Plasma concentration of chlorpromazine increased (consider reducing chlorpromazine dose)
Amoxicillin		
	Allopurinol	Increased risk of rash
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Methotrexate	Reduced excretion of methotrexate (increased risk of toxicity)
	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	
Amphotericin B		
	NOTE. Close monitoring required with concomitant administration of nephrotoxic drugs or cytotoxics.	
	Amikacin	Increased risk of nephrotoxicity
*	Ciclosporin	Increased risk of nephrotoxicity
*	Dexamethasone	Increased risk of hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions)
*	Digoxin	Hypokalaemia caused by amphotericin B increases cardiac toxicity of digoxin
	Fluconazole	Possible antagonism of effect of amphotericin B
	Flucytosine	Renal excretion of flucytosine decreased and cellular uptake increased (flucytosine toxicity possibly increased)
	Furosemide	Increased risk of hypokalaemia
	Gentamicin	Increased risk of nephrotoxicity
	Hydrochlorothiazide	Increased risk of hypokalaemia
*	Hydrocortisone	Increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions)
	Miconazole	Possibly antagonism of effects of amphotericin B
	Paromomycin	Possibly increased risk of nephrotoxicity
	Pentamidine	Possibly increased risk of nephrotoxicity
*	Prednisolone	Increased risk of hypokalaemia (avoid concomitant use unless prednisolone needed to control reactions)
	Streptomycin	Increased risk of nephrotoxicity
	Vancomycin	Possibly increased risk of nephrotoxicity
Ampicillin		
	Allopurinol	Increased risk of rash
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Methotrexate	Reduced excretion of methotrexate (increased risk of toxicity)
	Warfarin	Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of ampicillin
Antacids (Aluminium hydroxide; Magnesium hydroxide)		
	NOTE. Antacids should preferably not be taken at the same time as other drugs since they may impair absorption.	
	Acetylsalicylic acid	Excretion of acetylsalicylic acid increased by alkaline urine
	Azithromycin	Reduced absorption of azithromycin
	Chloroquine	Reduced absorption of chloroquine

	Chlorpromazine	Reduced absorption of chlorpromazine
	Ciprofloxacin	Reduced absorption of ciprofloxacin
	Digoxin	Possibly reduced absorption of digoxin
	Doxycycline	Reduced absorption of doxycycline
	Enalapril	Absorption of enalapril reduced
	Fluphenazine	Reduced absorption of fluphenazine
	Isoniazid	Reduced absorption of isoniazid
	Levofloxacin	Reduced absorption of levofloxacin
	Ofloxacin	Reduced absorption of ofloxacin
	Penicillamine	Reduced absorption of penicillamine
	Phenytoin	Reduced absorption of phenytoin
	Quinidine	Reduced quinidine excretion in alkaline urine (plasma quinidine concentration occasionally increased)
	Rifampicin	Reduced absorption of rifampicin
Artemether + lumefantrine		
*	Amitriptyline	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Azithromycin	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Chloroquine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Chlorpromazine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Ciprofloxacin	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Clomipramine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Erythromycin	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Fluconazole	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Fluoxetine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Fluphenazine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Grapefruit juice	Metabolism of artemether + lumefantrine may be inhibited (avoid concomitant use)
*	Haloperidol	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Indinavir	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Levofloxacin	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Lopinavir	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Mefloquine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Nelfinavir	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Ofloxacin	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Primaquine	Manufacturer of artemether + lumefantrine advises avoid concomitant use

*	Procainamide	Risk of ventricular arrhythmias; manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Proguanil	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Pyrimethamine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Quinidine	Risk of ventricular arrhythmias; manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Quinine	Risk of ventricular arrhythmias; manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Ritonavir	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Saquinavir	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Sulfadoxine + pyrimethamine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
Asparaginase		
	Vaccine, Live	Avoid use of live vaccines with asparaginase (impairment of immune response)
Atenolol		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amlodipine	Enhanced hypotensive effect
	Chlorpromazine	Enhanced hypotensive effect
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect
	Digoxin	Increased risk of AV block and bradycardia
	Enalapril	Enhanced hypotensive effect
*	Epinephrine	Severe hypertension
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glibenclamide	Atenolol may mask warning signs of hypoglycaemia such as tremor
	Glyceryl trinitrate	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of hypotensive effect
	Ibuprofen	Antagonism of hypotensive effect
	Insulins	Enhanced hypoglycaemic effect; atenolol may mask warning signs of hypoglycaemia such as tremor
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
*	Lidocaine	Increased myocardial depression (interaction less likely when lidocaine used topically)
	Mefloquine	Increased risk of bradycardia
	Metformin	Atenolol may mask warning signs of hypoglycaemia such as tremor
	Methyldopa	Enhanced hypotensive effect

*	Nifedipine	Enhanced hypotensive effect; possibly severe hypotension and heart failure
	Nitrous oxide	Enhanced hypotensive effect
	Pilocarpine	Increased risk of arrhythmias
	Prednisolone	Antagonism of hypotensive effect
*	Procainamide	Increased myocardial depression
*	Quinidine	Increased myocardial depression
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
*	Verapamil	Asystole, severe hypotension and heart failure

Atropine

NOTE. Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase adverse effects such as dry mouth, urine retention, and constipation, and can also lead to confusion especially in the elderly.

	Amitriptyline	Increased antimuscarinic adverse effects
	Chlorphenamine	Increased antimuscarinic adverse effects
	Chlorpromazine	Increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration)
	Clomipramine	Increased antimuscarinic adverse effects
	Fluphenazine	Increased antimuscarinic adverse effects (but reduced plasma fluphenazine concentration)
	Glyceryl trinitrate	Possibly reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Haloperidol	Possibly reduced effects of haloperidol
	Isosorbide dinitrate	Possibly reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Levodopa	Absorption of levodopa possibly reduced
	Metoclopramide	Antagonism of effects of metoclopramide on gastrointestinal activity
	Neostigmine	Antagonism of effects of neostigmine
	Pilocarpine	Antagonism of effects of pilocarpine
	Promethazine	Increased risk of antimuscarinic adverse effects
	Pyridostigmine	Antagonism of effects of pyridostigmine

Azathioprine

*	Allopurinol	Effects of azathioprine enhanced and toxicity increased; reduce dose of azathioprine
	Phenytoin	Possibly reduced absorption of phenytoin
*	Sulfamethoxazole + trimethoprim	Increased risk of haematological toxicity
	Sulfasalazine	Possibly increased risk of leukopenia
*	Trimethoprim	Increased risk of haematological toxicity
*	Vaccine, Live	Avoid use of live vaccines with azathioprine (impairment of immune response)
*	Warfarin	Anticoagulant effect possibly reduced

Azithromycin

	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of azithromycin

*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Ciclosporin	Possible inhibition of metabolism of ciclosporin (increased plasma concentration)
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Digoxin	Increased plasma concentration of digoxin (increased risk of toxicity)
	Ritonavir	Plasma concentration of azithromycin possibly increased
*	Warfarin	Possibly enhanced anticoagulant effect of warfarin
BCG vaccine		
	see Vaccine, Live	
Beclometasone		
	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)
	Methotrexate	Reduced excretion of methotrexate (increased risk of toxicity)
Biperiden		
	NOTE. Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase adverse effects such as dry mouth, urine retention, and constipation, and can also lead to confusion especially in the elderly.	
	Amitriptyline	Increased antimuscarinic adverse effects
	Chlorphenamine	Increased antimuscarinic adverse effects
	Chlorpromazine	Increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration)
	Clomipramine	Increased antimuscarinic adverse effects
	Fluphenazine	Increased antimuscarinic adverse effects (but reduced plasma fluphenazine concentration)
	Glyceryl trinitrate	Possibly reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Haloperidol	Possibly reduced effects of haloperidol
	Isosorbide dinitrate	Possibly reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Levodopa	Absorption of levodopa possibly reduced
	Metoclopramide	Antagonism of effects of metoclopramide on gastrointestinal activity
	Neostigmine	Antagonism of effects of neostigmine
	Pilocarpine	Antagonism of effects of pilocarpine
	Promethazine	Increased risk of antimuscarinic adverse effects
	Pyridostigmine	Antagonism of effects of pyridostigmine
Bleomycin		
*	Cisplatin	Increased pulmonary toxicity
*	Oxygen	Serious pulmonary toxicity in patients exposed to conventional oxygen concentrations during anaesthesia
	Phenytoin	Possibly reduced absorption of phenytoin

	Vaccine, Live	Avoid use of live vaccines with bleomycin (impairment of immune response)
*	Vinblastine	Increased risk of cardiovascular toxicity
Bupivacaine		
	Lidocaine	Increased myocardial depression (interaction less likely when lidocaine used topically)
	Procainamide	Increased myocardial depression
*	Propranolol	Increased risk of bupivacaine toxicity
	Quinidine	Increased myocardial depression
Calcium folinate		
	see Folic acid and Folinic acid	
Calcium gluconate		
	see Calcium salts	
Calcium salts		
	Ciprofloxacin	Reduced absorption of ciprofloxacin
	Dexamethasone	Reduced absorption of calcium salts
	Digoxin	Large intravenous doses of calcium salts can precipitate arrhythmias
	Ferrous salts	Reduced absorption of oral ferrous salts
	Hydrochlorothiazide	Increased risk of hypercalcaemia
	Hydrocortisone	Reduced absorption of calcium salts
	Levothyroxine	Reduced absorption of levothyroxine
	Prednisolone	Reduced absorption of calcium salts
	Sodium fluoride	Reduced absorption of sodium fluoride
	Zinc sulfate	Reduced absorption of zinc sulfate
Capreomycin		
	Amikacin	Increased risk of nephrotoxicity and ototoxicity
	Gentamicin	Increased risk of nephrotoxicity and ototoxicity
	Streptomycin	Increased risk of nephrotoxicity and ototoxicity
	Vancomycin	Increased risk of nephrotoxicity and ototoxicity
Carbamazepine		
*	Acetazolamide	Increased risk of hyponatraemia; acetazolamide increases plasma carbamazepine concentration
	Alcohol	Possibly enhanced CNS adverse effects of carbamazepine
	Alcuronium	Antagonism of muscle relaxant effect (recovery from neuromuscular blockade accelerated)
	Amiloride	Increased risk of hyponatraemia
*	Amitriptyline	Antagonism of anticonvulsant effect (convulsive threshold lowered); accelerated metabolism of amitriptyline (reduced plasma concentration; reduced antidepressant effect)
	Amlodipine	Probably reduced effect of amlodipine
	Chloroquine	Possibly increased risk of convulsions
*	Chlorpromazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Ciclosporin	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
*	Clomipramine	Antagonism of anticonvulsant effect (convulsive threshold lowered); accelerated metabolism of clomipramine (reduced plasma concentration; reduced antidepressant effect)
*	Contraceptives, Oral	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
*	Dexamethasone	Accelerated metabolism of dexamethasone (reduced effect)

	Doxycycline	Accelerated metabolism of doxycycline (reduced effect)
	Ergocalciferol	Ergocalciferol requirements possibly increased
*	Erythromycin	Increased plasma carbamazepine concentration
	Ethosuximide	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of ethosuximide possibly reduced
*	Fluoxetine	Plasma concentration of carbamazepine increased
*	Fluphenazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Furosemide	Increased risk of hyponatraemia
*	Haloperidol	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
	Hydrochlorothiazide	Increased risk of hyponatraemia
*	Hydrocortisone	Accelerated metabolism of hydrocortisone (reduced effect)
	Indinavir	Possibly reduced plasma indinavir concentration
*	Isoniazid	Increased plasma carbamazepine concentration (also isoniazid hepatotoxicity possibly increased)
*	Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
	Levothyroxine	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
	Lithium	Neurotoxicity may occur without increased plasma lithium concentration
*	Lopinavir	Possibly reduced plasma lopinavir concentration
	Mebendazole	Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection)
*	Medroxyprogesterone	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
*	Mefloquine	Antagonism of anticonvulsant effect
	Methadone	Reduced plasma concentration of methadone
	Miconazole	Plasma concentration of carbamazepine possibly increased
	Nelfinavir	Possibly reduced plasma nelfinavir concentration
	Nifedipine	Probably reduced effect of nifedipine
*	Norethisterone	Accelerated metabolism of norethisterone (reduced contraceptive effect)
*	Phenobarbital	May be enhanced toxicity without corresponding increase in antiepileptic effect; reduced plasma concentration of carbamazepine
*	Phenytoin	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of carbamazepine often lowered
	Praziquantel	Plasma praziquantel concentration reduced
*	Prednisolone	Accelerated metabolism of prednisolone (reduced effect)
*	Ritonavir	Plasma concentration possibly increased by ritonavir
	Saquinavir	Possibly reduced plasma saquinavir concentration
	Spironolactone	Increased risk of hyponatraemia
	Valproic acid	May be enhanced toxicity without corresponding increase in antiepileptic effect; reduced plasma concentration of valproic acid; plasma concentration of active metabolite of carbamazepine increased

	Vecuronium	Antagonism of muscle relaxant effect (recovery from neuromuscular blockade accelerated)
*	Verapamil	Enhanced effect of carbamazepine
*	Warfarin	Accelerated metabolism of warfarin (reduced anticoagulant effect)
Cefazolin		
*	Warfarin	Possibly enhanced anticoagulant effect
Cefixime		
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
*	Warfarin	Possibly enhanced anticoagulant effect
Ceftazidime		
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
*	Warfarin	Possibly enhanced anticoagulant effect
Ceftriaxone		
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
*	Warfarin	Possibly enhanced anticoagulant effect
Chlorambucil		
	Phenytoin	Possibly reduced absorption of phenytoin
	Vaccine, Live	Avoid use of live vaccines with chlorambucil (impairment of immune response)
Chloramphenicol		
*	Ciclosporin	Plasma concentration of ciclosporin possibly increased
*	Glibenclamide	Enhanced effect of glibenclamide
	Hydroxocobalamin	Response to hydroxocobalamin reduced
*	Phenobarbital	Metabolism of chloramphenicol accelerated (reduced plasma chloramphenicol concentration)
*	Phenytoin	Plasma phenytoin concentration increased (increased risk of toxicity)
	Rifampicin	Accelerated metabolism of chloramphenicol (reduced plasma chloramphenicol concentration)
*	Warfarin	Enhanced anticoagulant effect
Chloroquine		
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of chloroquine
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Carbamazepine	Possibly increased risk of convulsions
*	Ciclosporin	Increased plasma ciclosporin concentration (increased risk of toxicity)
*	Digoxin	Plasma digoxin concentration possibly increased
	Ethosuximide	Possibly increased risk of convulsions
*	Mefloquine	Increased risk of convulsions
	Neostigmine	Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine
	Phenytoin	Possible increased risk of convulsions
	Praziquantel	Plasma praziquantel concentration possibly reduced
	Pyridostigmine	Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of pyridostigmine

	Quinidine	Increased risk of ventricular arrhythmias
	Quinine	Increased risk of ventricular arrhythmias
*	Valproic acid	Possibly increased risk of convulsions
Chlorphenamine		
	Alcohol	Enhanced sedative effect
	Amitriptyline	Increased antimuscarinic and sedative effects
	Atropine	Increased antimuscarinic adverse effects
	Biperiden	Increased antimuscarinic adverse effects
	Clomipramine	Increased antimuscarinic and sedative effects
	Diazepam	Enhanced sedative effect
	Lopinavir	Possibly increased plasma concentration of chlorphenamine
Chlorpromazine		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced sedative effect
	Amiloride	Enhanced hypotensive effect
*	Amitriptyline	Increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
	Amlodipine	Enhanced hypotensive effect
	Amodiaquine	Plasma concentration of chlorpromazine increased (consider reducing chlorpromazine dose)
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of chlorpromazine
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Atenolol	Enhanced hypotensive effect
	Atropine	Increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration)
	Biperiden	Increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration)
*	Carbamazepine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Clomipramine	Increased antimuscarinic adverse effects; increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
	Codeine	Enhanced sedative and hypotensive effect
	Diazepam	Enhanced sedative effect
	Dopamine	Antagonism of hypertensive effect
	Enalapril	Enhanced hypotensive effect
	Ephedrine	Antagonism of hypertensive effect
	Epinephrine	Antagonism of hypertensive effect
*	Ethosuximide	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Furosemide	Enhanced hypotensive effect
	Glibenclamide	Possible antagonism of hypoglycaemic effect
	Glyceryl trinitrate	Enhanced hypotensive effect
*	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Isosorbide dinitrate	Enhanced hypotensive effect
*	Ketamine	Enhanced hypotensive effect
	Levodopa	Antagonism of effects of levodopa

	Lithium	Increased risk of extrapyramidal effects and possibility of neurotoxicity
	Methadone	Enhanced hypotensive and sedative effects
	Methyldopa	Enhanced hypotensive effect; increased risk of extrapyramidal effects
	Metoclopramide	Increased risk of extrapyramidal effects
	Morphine	Enhanced sedative and hypotensive effect
	Nifedipine	Enhanced hypotensive effect
*	Nitrous oxide	Enhanced hypotensive effect
*	Phenobarbital	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Procainamide	Increased risk of ventricular arrhythmias
*	Propranolol	Concomitant administration may increase plasma concentration of both drugs; enhanced hypotensive effect
*	Quinidine	Increased risk of ventricular arrhythmias
*	Ritonavir	Plasma concentration possibly increased by ritonavir
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
*	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
*	Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Verapamil	Enhanced hypotensive effect
Cholera vaccine (oral)		
	see Vaccine, Live	
Ciclosporin		
	Aciclovir	Increased risk of nephrotoxicity
	Allopurinol	Plasma ciclosporin concentration possibly increased (risk of nephrotoxicity)
*	Amikacin	Increased risk of nephrotoxicity
*	Amiloride	Increased risk of hyperkalaemia
*	Amphotericin B	Increased risk of nephrotoxicity
*	Azithromycin	Plasma concentration of ciclosporin possibly increased
*	Carbamazepine	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
*	Chloramphenicol	Plasma concentration of ciclosporin possibly increased
*	Chloroquine	Increased plasma ciclosporin concentration (increased risk of toxicity)
*	Ciprofloxacin	Increased risk of nephrotoxicity
*	Contraceptives, Oral	Plasma ciclosporin concentration increased by progestogens and possibly increased by estrogens
*	Digoxin	Increased plasma concentration of digoxin (increased risk of toxicity)
*	Doxorubicin	Increased risk of neurotoxicity
*	Doxycycline	Possibly increased plasma ciclosporin concentration
*	Enalapril	Increased risk of hyperkalaemia
*	Erythromycin	Increased plasma ciclosporin concentration (inhibition of metabolism of ciclosporin)
	Etoposide	Possibly increased plasma concentration of etoposide (increased risk of toxicity)

*	Fluconazole	Metabolism of ciclosporin inhibited (increased plasma concentration)
*	Gentamicin	Increased risk of nephrotoxicity
*	Grapefruit juice	Increased plasma ciclosporin concentration (risk of toxicity)
	Griseofulvin	Plasma ciclosporin concentration possibly reduced
	Hydrochlorothiazide	Increased risk of nephrotoxicity and possibly hypermagnesaemia
*	Ibuprofen	Increased risk of nephrotoxicity
*	Levofloxacin	Increased risk of nephrotoxicity
*	Levonorgestrel	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
*	Medroxyprogesterone	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
*	Methotrexate	Increased toxicity
*	Metoclopramide	Plasma ciclosporin concentration increased
*	Nelfinavir	Possibly increased plasma ciclosporin concentration
	Nifedipine	Possibly increased plasma nifedipine concentration (increased risk of adverse effects such as gingival hyperplasia)
*	Norethisterone	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
*	Ofloxacin	Increased risk of nephrotoxicity
*	Phenobarbital	Metabolism of ciclosporin accelerated (reduced effect)
*	Phenytoin	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
*	Potassium salts	Increased risk of hyperkalaemia
	Prednisolone	Increased plasma concentration of prednisolone
*	Rifampicin	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
*	Ritonavir	Plasma concentration possibly increased by ritonavir
*	Saquinavir	Plasma concentration of both ciclosporin and saquinavir increased
*	Silver sulfadiazine	Increased risk of nephrotoxicity; possibly reduced plasma concentration of ciclosporin
*	Simvastatin	Increased risk of myopathy
*	Spironolactone	Increased risk of hyperkalaemia
*	Streptomycin	Increased risk of nephrotoxicity
*	Sulfadiazine	Plasma ciclosporin concentration possibly reduced; increased risk of nephrotoxicity
*	Sulfadoxine + pyrimethamine	Increased risk of nephrotoxicity
*	Sulfamethoxazole + trimethoprim	Increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim
*	Trimethoprim	Increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim
*	Vaccine, Live	Avoid use of live vaccines with ciclosporin (impairment of immune response)
*	Vancomycin	Increased risk of nephrotoxicity
*	Verapamil	Increased plasma ciclosporin concentration

Ciprofloxacin		
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of ciprofloxacin
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Calcium salts	Reduced absorption of ciprofloxacin
*	Ciclosporin	Increased risk of nephrotoxicity
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Dairy products	Reduced absorption of ciprofloxacin
	Ferrous salts	Absorption of ciprofloxacin reduced by oral ferrous salts
	Glibenclamide	Possibly enhanced effect of glibenclamide
*	Ibuprofen	Possibly increased risk of convulsions
	Morphine	Manufacturer of ciprofloxacin advises avoid premedication with morphine (reduced plasma ciprofloxacin concentration) when ciprofloxacin used for surgical prophylaxis
	Phenytoin	Plasma phenytoin concentration can be increased or decreased by ciprofloxacin
*	Warfarin	Enhanced anticoagulant effect
	Zinc sulfate	Reduced absorption of ciprofloxacin
Cisplatin		
	Acetazolamide	Increased risk of nephrotoxicity and ototoxicity
*	Amikacin	Increased risk of nephrotoxicity and possibly of ototoxicity
	Amiloride	Increased risk of nephrotoxicity and ototoxicity
*	Bleomycin	Increased pulmonary toxicity
	Furosemide	Increased risk of nephrotoxicity and ototoxicity
*	Gentamicin	Increased risk of nephrotoxicity and possibly of ototoxicity
	Hydrochlorothiazide	Increased risk of nephrotoxicity and ototoxicity
*	Methotrexate	Risk of pulmonary toxicity
	Paromomycin	Increased risk of ototoxicity
	Phenytoin	Reduced absorption of phenytoin
	Spironolactone	Increased risk of nephrotoxicity and ototoxicity
*	Streptomycin	Increased risk of nephrotoxicity and possibly of ototoxicity
	Vaccine, Live	Avoid use of live vaccines with cisplatin (impairment of immune response)
	Vancomycin	Increased risk of nephrotoxicity and possibly of ototoxicity
Clindamycin		
*	Alcuronium	Enhanced muscle relaxant effect
	Neostigmine	Antagonism of effects of neostigmine
	Pyridostigmine	Antagonism of effects of pyridostigmine
*	Suxamethonium	Enhanced effects of suxamethonium
*	Vecuronium	Enhanced muscle relaxant effect
Clomipramine		
	Acetazolamide	Increased risk of postural hypotension
*	Alcohol	Enhanced sedative effect
	Amiloride	Increased risk of postural hypotension
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Atropine	Increased antimuscarinic adverse effects
	Biperiden	Increased antimuscarinic adverse effects

*	Carbamazepine	Antagonism of anticonvulsant effect (convulsive threshold lowered); accelerated metabolism of clomipramine (reduced plasma concentration; reduced antidepressant effect)
	Chlorphenamine	Increased antimuscarinic and sedative effects
*	Chlorpromazine	Increased antimuscarinic adverse effects; increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
	Codeine	Possibly increased sedation
	Contraceptives, Oral	Antagonism of antidepressant effect by estrogens but adverse effects of clomipramine possibly increased due to increased plasma concentration of clomipramine
	Diazepam	Enhanced sedative effect
*	Epinephrine	Increased risk of hypertension and arrhythmias (but local anaesthetics which contain epinephrine appear to be safe)
*	Ethosuximide	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Fluphenazine	Increased antimuscarinic adverse effects; increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
	Furosemide	Increased risk of postural hypotension
	Glyceryl trinitrate	Reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
*	Haloperidol	Increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
	Halothane	Increased risk of arrhythmias and hypotension
	Hydrochlorothiazide	Increased risk of postural hypotension
	Isosorbide dinitrate	Reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Ketamine	Increased risk of arrhythmias and hypotension
	Levothyroxine	Possibly enhanced effects of clomipramine
	Lithium	Risk of toxicity
	Methadone	Sedative effects possibly increased
	Morphine	Possibly increased sedation
	Nitrous oxide	Increased risk of arrhythmias and hypotension
*	Phenobarbital	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of clomipramine possibly accelerated (reduced plasma concentration)
*	Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered); possibly reduced plasma clomipramine concentration
*	Procainamide	Increased risk of ventricular arrhythmias
	Promethazine	Increased antimuscarinic and sedative effects
*	Quinidine	Increased risk of ventricular arrhythmias
	Rifampicin	Plasma concentration of clomipramine possibly reduced
*	Ritonavir	Plasma concentration possibly increased by ritonavir
	Spironolactone	Increased risk of postural hypotension
	Thiopental	Increased risk of arrhythmias and hypotension
*	Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Verapamil	Possibly increased plasma concentration of clomipramine
	Warfarin	Enhanced or reduced anticoagulant effect

Clotrimazole		
*	Simvastatin	Increased risk of myopathy
Cloxacillin		
	see Benzylpenicillin	
Codeine		
	Alcohol	Enhanced sedative and hypotensive effect
	Amitriptyline	Possibly increased sedation
	Chlorpromazine	Enhanced sedative and hypotensive effect
	Clomipramine	Possibly increased sedation
	Diazepam	Enhanced sedative effect
	Fluphenazine	Enhanced sedative and hypotensive effect
	Haloperidol	Enhanced sedative and hypotensive effect
	Metoclopramide	Antagonism of effect of metoclopramide on gastrointestinal activity
*	Ritonavir	Ritonavir possibly increases plasma concentration of codeine
Contraceptives, Oral		
	NOTE. Interactions of combined (estrogen and progestogen) oral contraceptives may also apply to combined parenteral contraceptives.	
	Acetazolamide	Antagonism of diuretic effect by estrogens
	Amiloride	Antagonism of diuretic effect by estrogens
	Amitriptyline	Antagonism of antidepressant effect by estrogens but adverse effects of amitriptyline possibly increased due to increased plasma concentration of amitriptyline
	Amlodipine	Antagonism of hypotensive effect by estrogens
	Amoxicillin	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Ampicillin	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Atenolol	Antagonism of hypotensive effect by estrogens
	Azithromycin	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Benzylpenicillin	Contraceptive effect of estrogens possibly reduced (risk probably small)
*	Carbamazepine	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
	Cefixime	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Ceftazidime	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Ceftriaxone	Contraceptive effect of estrogens possibly reduced (risk probably small)
*	Ciclosporin	Plasma ciclosporin concentration increased by progestogens and possibly increased by estrogens
	Ciprofloxacin	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Clomipramine	Antagonism of antidepressant effect by estrogens but adverse effects of clomipramine possibly increased due to increased plasma concentration of clomipramine
	Dexamethasone	Oral contraceptives containing estrogens increase plasma concentration of dexamethasone

	Doxycycline	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Efavirenz	Efficacy of estrogen-containing oral contraceptives possibly reduced
	Enalapril	Antagonism of hypotensive effect by estrogens
	Erythromycin	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Fluconazole	Anecdotal reports of failure of estrogen-containing contraceptives
	Furosemide	Antagonism of diuretic effect by estrogens
	Glibenclamide	Antagonism of hypoglycaemic effect by estrogens and progestogens
	Glyceryl trinitrate	Antagonism of hypotensive effect by estrogens
*	Griseofulvin	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
	Hydralazine	Antagonism of hypotensive effect by estrogens
	Hydrochlorothiazide	Antagonism of diuretic effect by estrogens
	Hydrocortisone	Oral contraceptives containing estrogens increase plasma concentration of hydrocortisone
	Imipenem + cilastatin	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Insulins	Antagonism of hypoglycaemic effect by estrogens and progestogens
	Isosorbide dinitrate	Antagonism of hypotensive effect by estrogens
	Levofloxacin	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Metformin	Antagonism of hypoglycaemic effect by estrogens and progestogens
	Methyldopa	Antagonism of hypotensive effect by estrogens
	Metronidazole	Contraceptive effect of estrogens possibly reduced (risk probably small)
*	Nelfinavir	Accelerated metabolism of estrogens (reduced contraceptive effect); nelfinavir possibly reduces contraceptive effect of progestogens
*	Nevirapine	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
	Nifedipine	Antagonism of hypotensive effect by estrogens
	Ofloxacin	Contraceptive effect of estrogens possibly reduced (risk probably small)
*	Phenobarbital	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
	Phenoxymethylpenicillin	Contraceptive effect of estrogens possibly reduced (risk probably small)
*	Phenytoin	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
	Prednisolone	Oral contraceptives containing estrogens increase plasma concentration of prednisolone
	Propranolol	Antagonism of hypotensive effect by estrogens
*	Rifampicin	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
*	Ritonavir	Accelerated metabolism of estrogens (reduced contraceptive effect)
	Sodium nitroprusside	Antagonism of hypotensive effect by estrogens
	Spironolactone	Antagonism of diuretic effect by estrogens

	Verapamil	Antagonism of hypotensive effect by estrogens
*	Warfarin	Antagonism of anticoagulant effect by estrogens and progestogens
Cyclophosphamide		
	Phenytoin	Possibly reduced absorption of phenytoin
	Suxamethonium	Enhanced effect of suxamethonium
	Vaccine, Live	Avoid use of live vaccines with cyclophosphamide (impairment of immune response)
Cycloserine		
*	Alcohol	Increased risk of convulsions
	Isoniazid	Increased risk of CNS toxicity
Cytarabine		
	Flucytosine	Plasma flucytosine concentration possibly reduced
	Phenytoin	Reduced absorption of phenytoin
	Vaccine, Live	Avoid use of live vaccines with cytarabine (impairment of immune response)
Dacarbazine		
	Phenytoin	Possibly reduced absorption of phenytoin
	Vaccine, Live	Avoid use of live vaccines with dacarbazine (impairment of immune response)
Dactinomycin		
	Phenytoin	Possibly reduced absorption of phenytoin
	Vaccine, Live	Avoid use of live vaccines with dactinomycin (impairment of immune response)
Dairy products		
	Ciprofloxacin	Reduced absorption of ciprofloxacin
Dapsone		
	Rifampicin	Reduced plasma dapsone concentration
	Sulfamethoxazole + trimethoprim	Plasma concentration of both dapsone and trimethoprim may increase with concomitant use
	Trimethoprim	Plasma concentration of both dapsone and trimethoprim may increase with concomitant use
Daunorubicin		
	Phenytoin	Possibly reduced absorption of phenytoin
	Vaccine, Live	Avoid use of live vaccines with daunorubicin (impairment of immune response)
Dexamethasone		
	Acetazolamide	Increased risk of hypokalaemia; antagonism of diuretic effect
	Acetylsalicylic acid	Increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma salicylate concentration
	Albendazole	Plasma albendazole concentration possibly increased
	Amiloride	Antagonism of diuretic effect
	Amlodipine	Antagonism of hypotensive effect
*	Amphotericin B	Increased risk of hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions)
	Atenolol	Antagonism of hypotensive effect
	Calcium salts	Reduced absorption of calcium salts
*	Carbamazepine	Accelerated metabolism of dexamethasone (reduced effect)
	Contraceptives, Oral	Oral contraceptives containing estrogens increase plasma concentration of dexamethasone
	Digoxin	Increased risk of hypokalaemia
	Enalapril	Antagonism of hypotensive effect

	Ephedrine	Metabolism of dexamethasone accelerated
	Erythromycin	Erythromycin possibly inhibits metabolism of dexamethasone
	Furosemide	Antagonism of diuretic effect; increased risk of hypokalaemia
	Glibenclamide	Antagonism of hypoglycaemic effect
	Glyceryl trinitrate	Antagonism of hypotensive effect
	Hydralazine	Antagonism of hypotensive effect
	Hydrochlorothiazide	Antagonism of diuretic effect; increased risk of hypokalaemia
	Ibuprofen	Increased risk of gastrointestinal bleeding and ulceration
	Indinavir	Possibly reduced plasma indinavir concentration
	Insulins	Antagonism of hypoglycaemic effect
	Isosorbide dinitrate	Antagonism of hypotensive effect
*	Lopinavir	Possibly reduced plasma lopinavir concentration
	Metformin	Antagonism of hypoglycaemic effect
*	Methotrexate	Increased risk of haematological toxicity
	Methyldopa	Antagonism of hypotensive effect
	Mifepristone	Possibly reduced effects of dexamethasone for 3–4 days
	Nifedipine	Antagonism of hypotensive effect
*	Phenobarbital	Metabolism of dexamethasone accelerated (reduced effect)
*	Phenytoin	Metabolism of dexamethasone accelerated (reduced effect)
	Praziquantel	Plasma praziquantel concentration reduced
	Propranolol	Antagonism of hypotensive effect
*	Rifampicin	Accelerated metabolism of dexamethasone (reduced effect)
	Ritonavir	Plasma concentration possibly increased by ritonavir
	Salbutamol	Increased risk of hypokalaemia if high doses of salbutamol given with dexamethasone
	Saquinavir	Possibly reduced plasma saquinavir concentration
	Sodium nitroprusside	Antagonism of hypotensive effect
	Spironolactone	Antagonism of diuretic effect
	Vaccine, Influenza	High doses of dexamethasone impair immune response
*	Vaccine, Live	High doses of dexamethasone impair immune response; avoid use of live vaccines with dexamethasone
	Verapamil	Antagonism of hypotensive effect
*	Warfarin	Anticoagulant effect possibly enhanced or reduced (high-dose dexamethasone enhances anticoagulant effect)
Diazepam		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced sedative effect
	Amiloride	Enhanced hypotensive effect
	Amitriptyline	Enhanced sedative effect
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Chlorphenamine	Enhanced sedative effect
	Chlorpromazine	Enhanced sedative effect
	Clomipramine	Enhanced sedative effect
	Codeine	Enhanced sedative effect
	Enalapril	Enhanced hypotensive effect
	Fluphenazine	Enhanced sedative effect
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Haloperidol	Enhanced sedative effect
	Halothane	Enhanced sedative effect

	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Isoniazid	Metabolism of diazepam inhibited
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced sedative effect
	Levodopa	Possibly antagonism of levodopa effects
	Methadone	Increased sedative effect
	Methyldopa	Enhanced hypotensive effect
	Morphine	Enhanced sedative effect
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced sedative effect
	Phenytoin	Plasma phenytoin concentration possibly increased or decreased by diazepam
	Promethazine	Enhanced sedative effect
	Propranolol	Enhanced hypotensive effect
	Rifampicin	Metabolism of diazepam accelerated (reduced plasma concentration)
*	Ritonavir	Plasma concentration possibly increased by ritonavir (risk of extreme sedation and respiratory depression—avoid concomitant use)
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Thiopental	Enhanced sedative effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect
Didanosine		
	NOTE. Antacids present in buffered tablet formulation may affect absorption of other drugs; *see also* Antacids.	
	Allopurinol	Possibly increased plasma concentration of didanosine
*	Ribavirin	Increased risk of adverse effects; manufacturer of ribavirin advises avoid concomitant use
*	Stavudine	Increased risk of adverse effects
	Tenofovir	Plasma concentration of didanosine increased (increased risk of toxicity — avoid concomitant use)
Digoxin		
*	Acetazolamide	Hypokalaemia caused by acetazolamide increases cardiac toxicity of digoxin
*	Amphotericin B	Hypokalaemia caused by amphotericin B increases cardiac toxicity of digoxin
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Possibly reduced absorption of digoxin
	Atenolol	Increased risk of AV block and bradycardia
	Azithromycin	Increased plasma concentration of digoxin (increased risk of toxicity)
	Calcium salts	Large intravenous doses of calcium salts can precipitate arrhythmias
*	Chloroquine	Plasma digoxin concentration possibly increased
*	Ciclosporin	Increased plasma concentration of digoxin (increased risk of toxicity)
	Dexamethasone	Increased risk of hypokalaemia

	Erythromycin	Increased plasma concentration of digoxin (increased risk of toxicity)
*	Furosemide	Hypokalaemia caused by furosemide increases cardiac toxicity of digoxin
	Gentamicin	Possibly increased plasma concentration of digoxin
*	Hydrochlorothiazide	Hypokalaemia caused by hydrochlorothiazide increases cardiac toxicity of digoxin
	Hydrocortisone	Increased risk of hypokalaemia
	Ibuprofen	Possibly exacerbation of heart failure, reduced renal function, and increased plasma digoxin concentration
	Mefloquine	Possibly increased risk of bradycardia
*	Nifedipine	Possibly increased plasma concentration of digoxin
	Penicillamine	Plasma concentration of digoxin possibly reduced
	Phenytoin	Plasma concentration of digoxin possibly reduced
	Prednisolone	Increased risk of hypokalaemia
	Propranolol	Increased risk of AV block and bradycardia
*	Quinidine	Plasma concentration of digoxin increased (halve dose of digoxin)
*	Quinine	Plasma concentration of digoxin increased
	Rifampicin	Plasma concentration of digoxin possibly reduced
	Salbutamol	Possibly reduced plasma concentration of digoxin
*	Spironolactone	Plasma concentration of digoxin increased
	Sulfamethoxazole + trimethoprim	Plasma concentration of digoxin possibly increased
	Sulfasalazine	Absorption of digoxin possibly reduced
	Suxamethonium	Risk of ventricular arrhythmias
	Timolol	Increased AV block and bradycardia
	Trimethoprim	Plasma concentration of digoxin possibly increased
*	Verapamil	Increased plasma concentration of digoxin; increased AV block and bradycardia
Dimercaprol		
*	Ferrous salts	Avoid concomitant use
Dopamine		
	Chlorpromazine	Antagonism of hypertensive effect
	Ergometrine	Increased risk of ergotism
	Fluphenazine	Antagonism of hypertensive effect
	Haloperidol	Antagonism of hypertensive effect
Doxorubicin		
	Ciclosporin	Increased risk of neurotoxicity
	Phenytoin	Possibly reduced absorption of phenytoin
	Stavudine	Doxorubicin may inhibit effect of stavudine
	Vaccine, Live	Avoid use of live vaccines with doxorubicin (impairment of immune response)
Doxycycline		
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of doxycycline
	Carbamazepine	Accelerated metabolism of doxycycline (reduced effect)
*	Ciclosporin	Possibly increased plasma ciclosporin concentration
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Ferrous salts	Absorption of oral ferrous salts reduced by doxycycline; absorption of doxycycline reduced by oral ferrous salts

	Methotrexate	Increased risk of methotrexate toxicity
	Phenobarbital	Metabolism of doxycycline accelerated (reduced plasma concentration)
	Phenytoin	Increased metabolism of doxycycline (reduced plasma concentration)
	Rifampicin	Plasma doxycycline concentration possibly reduced
*	Warfarin	Anticoagulant effect possibly enhanced
Efavirenz		
	Contraceptives, Oral	Efficacy of estrogen-containing oral contraceptives possibly reduced
*	Ergometrine	Increased risk of ergotism (avoid concomitant use)
	Grapefruit juice	Plasma concentration of efavirenz possibly increased
	Indinavir	Efavirenz reduces plasma concentration of indinavir
*	Lopinavir	Plasma concentration of lopinavir reduced
	Methadone	Reduced plasma concentration of methadone
	Nevirapine	Plasma efavirenz concentration reduced
	Rifampicin	Reduced plasma concentration of efavirenz (increase efavirenz dose)
	Ritonavir	Increased risk of toxicity (monitor liver function tests)
	Saquinavir	Efavirenz significantly reduces plasma concentration of saquinavir
Emtricitabine		
	Lamivudine	No information available; manufacturer advises avoid concomitant use
Enalapril		
*	Acetazolamide	Enhanced hypotensive effect
	Acetylsalicylic acid	Antagonism of hypotensive effect; risk of renal impairment when acetylsalicylic acid given in doses of over 300 mg daily
	Alcohol	Enhanced hypotensive effect
*	Amiloride	Enhanced hypotensive effect; increased risk of severe hyperkalaemia
	Amlodipine	Enhanced hypotensive effect
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Absorption of enalapril reduced
	Atenolol	Enhanced hypotensive effect
	Chlorpromazine	Enhanced hypotensive effect
*	Ciclosporin	Increased risk of hyperkalaemia
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect
	Fluphenazine	Enhanced hypotensive effect
*	Furosemide	Enhanced hypotensive effect
	Glibenclamide	Hypoglycaemic effect possibly enhanced
	Glyceryl trinitrate	Enhanced hypotensive effect
	Haloperidol	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Heparin	Increased risk of hyperkalaemia
	Hydralazine	Enhanced hypotensive effect
*	Hydrochlorothiazide	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of hypotensive effect

	Ibuprofen	Antagonism of hypotensive effect; increased risk of renal impairment
	Insulins	Hypoglycaemic effect possibly enhanced
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
*	Lithium	Enalapril reduces excretion of lithium (increased plasma lithium concentration)
	Metformin	Hypoglycaemic effect possibly enhanced
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
*	Potassium salts	Increased risk of severe hyperkalaemia
	Prednisolone	Antagonism of hypotensive effect
	Propranolol	Enhanced hypotensive effect
	Sodium nitroprusside	Enhanced hypotensive effect
*	Spironolactone	Enhanced hypotensive effect; increased risk of severe hyperkalaemia (monitor plasma potassium concentration with low-dose spironolactone in heart failure)
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect
Ephedrine		
	Chlorpromazine	Antagonism of hypertensive effect
	Dexamethasone	Metabolism of dexamethasone accelerated
	Fluphenazine	Antagonism of hypertensive effect
	Haloperidol	Antagonism of hypertensive effect
	Oxytocin	Risk of hypertension due to enhanced vasopressor effect of ephedrine
Epinephrine		
*	Amitriptyline	Increased risk of hypertension and arrhythmias (but local anaesthetics which contain epinephrine appear to be safe)
*	Atenolol	Severe hypertension
	Chlorpromazine	Antagonism of hypertensive effect
*	Clomipramine	Increased risk of hypertension and arrhythmias (but local anaesthetics which contain epinephrine appear to be safe)
	Fluphenazine	Antagonism of hypertensive effect
	Haloperidol	Antagonism of hypertensive effect
*	Halothane	Risk of arrhythmias
	Oxytocin	Risk of hypertension due to enhanced vasopressor effect of epinephrine
*	Propranolol	Severe hypertension
*	Timolol	Severe hypertension
Ergocalciferol		
	Carbamazepine	Ergocalciferol requirements possibly increased
	Hydrochlorothiazide	Increased risk of hypercalcaemia
	Phenobarbital	Ergocalciferol requirements possibly increased
	Phenytoin	Ergocalciferol requirements possibly increased
Ergometrine		
	Dopamine	Increased risk of ergotism
*	Efavirenz	Increased risk of ergotism (avoid concomitant use)
	Halothane	Reduced effect of ergometrine on parturient uterus

Erythromycin		
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Carbamazepine	Increased plasma carbamazepine concentration
*	Ciclosporin	Increased plasma ciclosporin concentration (inhibition of metabolism of ciclosporin)
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Dexamethasone	Erythromycin possibly inhibits metabolism of dexamethasone
	Digoxin	Increased plasma concentration of digoxin (increased risk of toxicity)
	Hydrocortisone	Erythromycin possibly inhibits metabolism of hydrocortisone
	Prednisolone	Erythromycin possibly inhibits metabolism of prednisolone
*	Quinidine	Increased risk of ventricular arrhythmias with parenteral erythromycin
	Ritonavir	Plasma concentration possibly increased by ritonavir
*	Simvastatin	Increased risk of myopathy
	Valproic acid	Metabolism of valproic acid possibly inhibited (increased plasma concentration)
*	Verapamil	Possible inhibition of metabolism of verapamil (increased risk of toxicity)
*	Vinblastine	Increased toxicity of vinblastine (avoid concomitant use)
*	Warfarin	Enhanced anticoagulant effect
Estradiol cypionate		
	see Contraceptives, Oral	
Ethinylestradiol		
	see Contraceptives, Oral	
Ethosuximide		
*	Amitriptyline	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Carbamazepine	May be enhanced toxicity without corresponding increase in antiepileptic effect; possibly reduced plasma concentration of ethosuximide
	Chloroquine	Possibly increased risk of convulsions
*	Chlorpromazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Clomipramine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Fluphenazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Haloperidol	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Isoniazid	Metabolism of ethosuximide inhibited (increased plasma ethosuximide concentration and risk of toxicity)
*	Mefloquine	Antagonism of anticonvulsant effect
	Phenobarbital	May be enhanced toxicity without corresponding increase in antiepileptic effect; possibly reduced plasma concentration of ethosuximide

*	Phenytoin	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin possibly increased; plasma concentration of ethosuximide possibly reduced
	Valproic acid	May be enhanced toxicity without corresponding increase in antiepileptic effect; possibly increased plasma concentration of ethosuximide
Etoposide		
	Ciclosporin	Possibly increased plasma concentration of etoposide (increased risk of toxicity)
	Phenobarbital	Possibly reduced plasma concentration of etoposide
	Phenytoin	Possibly reduced absorption of phenytoin and possibly reduced plasma concentration of etoposide
	Vaccine, Live	Avoid use of live vaccines with etoposide (impairment of immune response)
*	Warfarin	Possibly enhanced anticoagulant effect
Ferrous salts		
	Calcium salts	Reduced absorption of oral ferrous salts
	Ciprofloxacin	Absorption of ciprofloxacin reduced by oral ferrous salts
*	Dimercaprol	Avoid concomitant use
	Doxycycline	Absorption of oral ferrous salts reduced by doxycycline; absorption of doxycycline reduced by oral ferrous salts
	Levodopa	Absorption of levodopa may be reduced by oral ferrous salts
	Levofloxacin	Absorption of levofloxacin reduced by oral ferrous salts
	Levothyroxine	Absorption of levothyroxine reduced by oral ferrous salts (give at least 2 hours apart)
	Methyldopa	Oral ferrous salts reduce hypotensive effect of methyldopa
	Ofloxacin	Absorption of ofloxacin reduced by oral ferrous salts
	Penicillamine	Oral ferrous salts reduce absorption of penicillamine
	Zinc sulfate	Absorption of zinc and of oral ferrous salts reduced
Ferrous salt + folic acid		
	see Ferrous salts; Folic acid	
Fluconazole		
	Amphotericin B	Possible antagonism of effect of amphotericin B
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Ciclosporin	Metabolism of ciclosporin inhibited (increased plasma concentration)
	Contraceptives, Oral	Anecdotal reports of failure of estrogen-containing contraceptives
*	Glibenclamide	Plasma concentration of glibenclamide increased
	Hydrochlorothiazide	Plasma concentration of fluconazole increased
*	Nevirapine	Increased plasma concentration of nevirapine
*	Phenytoin	Plasma concentration of phenytoin increased (consider reducing dose of phenytoin)
*	Rifampicin	Accelerated metabolism of fluconazole (reduced plasma concentration)
	Ritonavir	Plasma concentration of fluconazole increased by ritonavir
	Saquinavir	Plasma concentration of saquinavir possibly increased
*	Warfarin	Enhanced anticoagulant effect
*	Zidovudine	Increased plasma concentration of zidovudine (increased risk of toxicity)

Flucytosine		
	Amphotericin B	Renal excretion of flucytosine decreased and cellular uptake increased (flucytosine toxicity possibly increased)
	Cytarabine	Plasma flucytosine concentration possibly reduced
Fluorouracil		
	Metronidazole	Metabolism of fluorouracil inhibited (increased toxicity)
	Phenytoin	Metabolism of phenytoin possibly inhibited (increased risk of toxicity)
	Vaccine, Live	Avoid use of live vaccines with fluorouracil (impairment of immune response)
*	Warfarin	Anticoagulant effect possibly enhanced
Fluoxetine		
*	Acetylsalicylic acid	Increased risk of bleeding
	Alcohol	Possibly increased sedation
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Carbamazepine	Plasma concentration of carbamazepine increased
*	Haloperidol	Plasma concentration of haloperidol increased
*	Ibuprofen	Increased risk of bleeding
*	Lithium	Increased risk of CNS effects (lithium toxicity reported)
	Phenobarbital	Antagonism of anticonvulsive effect (convulsive threshold lowered)
*	Phenytoin	Plasma concentration of phenytoin increased
*	Ritonavir	Plasma concentration of fluoxetine possibly increased
*	Warfarin	Anticoagulant effect possibly enhanced
Fluphenazine		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced sedative effect
	Amiloride	Enhanced hypotensive effect
*	Amitriptyline	Increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
	Amlodipine	Enhanced hypotensive effect
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of fluphenazine
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Atenolol	Enhanced hypotensive effect
	Atropine	Increased antimuscarinic adverse effects (but reduced plasma fluphenazine concentration)
	Biperiden	Increased antimuscarinic adverse effects (but reduced plasma fluphenazine concentration)
*	Carbamazepine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Clomipramine	Increased antimuscarinic adverse effects; increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
	Codeine	Enhanced sedative and hypotensive effect
	Diazepam	Enhanced sedative effect
	Dopamine	Antagonism of hypertensive effect
	Enalapril	Enhanced hypotensive effect
	Ephedrine	Antagonism of hypertensive effect

	Epinephrine	Antagonism of hypertensive effect
*	Ethosuximide	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Furosemide	Enhanced hypotensive effect
	Glibenclamide	Possible antagonism of hypoglycaemic effect
	Glyceryl trinitrate	Enhanced hypotensive effect
*	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Isosorbide dinitrate	Enhanced hypotensive effect
*	Ketamine	Enhanced hypotensive effect
	Levodopa	Antagonism of effects of levodopa
	Lithium	Increased risk of extrapyramidal effects and possibility of neurotoxicity
	Methadone	Enhanced hypotensive and sedative effects
	Methyldopa	Enhanced hypotensive effect; increased risk of extrapyramidal effects
	Metoclopramide	Increased risk of extrapyramidal effects
	Morphine	Enhanced sedative and hypotensive effect
	Nifedipine	Enhanced hypotensive effect
*	Nitrous oxide	Enhanced hypotensive effect
*	Phenobarbital	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Procainamide	Increased risk of ventricular arrhythmias
	Propranolol	Enhanced hypotensive effect
*	Quinidine	Increased risk of ventricular arrhythmias
*	Ritonavir	Plasma concentration possibly increased by ritonavir
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
*	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
*	Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Verapamil	Enhanced hypotensive effect
Folic acid; folinic acid		
	Phenobarbital	Plasma concentration of phenobarbital possibly reduced
	Phenytoin	Plasma phenytoin concentration possibly reduced
	Sulfasalazine	Possibly reduced absorption of folic acid
Furosemide		
	Acetazolamide	Increased risk of hypokalaemia
	Alcohol	Enhanced hypotensive effect
*	Amikacin	Increased risk of ototoxicity
	Amitriptyline	Increased risk of postural hypotension
	Amlodipine	Enhanced hypotensive effect
	Amphotericin B	Increased risk of hypokalaemia
	Atenolol	Enhanced hypotensive effect
	Carbamazepine	Increased risk of hyponatraemia
	Chlorpromazine	Enhanced hypotensive effect
	Cisplatin	Increased risk of nephrotoxicity and ototoxicity
	Clomipramine	Increased risk of postural hypotension
	Contraceptives, Oral	Antagonism of diuretic effect by estrogens

	Dexamethasone	Antagonism of diuretic effect; increased risk of hypokalaemia
	Diazepam	Enhanced hypotensive effect
*	Digoxin	Hypokalaemia caused by furosemide increases cardiac toxicity of digoxin
*	Enalapril	Enhanced hypotensive effect
	Fluphenazine	Enhanced hypotensive effect
*	Gentamicin	Increased risk of ototoxicity
	Glibenclamide	Antagonism of hypoglycaemic effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Increased risk of hypokalaemia
	Hydrocortisone	Antagonism of diuretic effect; increased risk of hypokalaemia
	Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
	Insulins	Antagonism of hypoglycaemic effect
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
*	Lidocaine	Action of lidocaine antagonized by hypokalaemia caused by furosemide (interaction less likely when lidocaine used topically)
*	Lithium	Reduced lithium excretion (increased plasma lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide
	Metformin	Antagonism of hypoglycaemic effect
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
	Paromomycin	Increased risk of ototoxicity
	Prednisolone	Antagonism of diuretic effect; increased risk of hypokalaemia
	Propranolol	Enhanced hypotensive effect
*	Quinidine	Cardiac toxicity of quinidine increased by hypokalaemia caused by furosemide
	Salbutamol	Increased risk of hypokalaemia with high doses of salbutamol
	Sodium nitroprusside	Enhanced hypotensive effect
*	Streptomycin	Increased risk of ototoxicity
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
*	Vancomycin	Increased risk of ototoxicity
	Verapamil	Enhanced hypotensive effect
Gentamicin		
*	Alcuronium	Enhanced muscle relaxant effect
	Amphotericin B	Increased risk of nephrotoxicity
	Capreomycin	Increased risk of nephrotoxicity and ototoxicity
*	Ciclosporin	Increased risk of nephrotoxicity
*	Cisplatin	Increased risk of nephrotoxicity and possibly of ototoxicity
	Digoxin	Possibly increased plasma concentration of digoxin
*	Furosemide	Increased risk of ototoxicity
*	Neostigmine	Antagonism of effect of neostigmine

*	Pyridostigmine	Antagonism of effect of pyridostigmine
*	Suxamethonium	Enhanced muscle relaxant effect
	Vancomycin	Increased risk of nephrotoxicity and ototoxicity
*	Vecuronium	Enhanced muscle relaxant effect
Glibenclamide		
	Alcohol	Enhanced hypoglycaemic effect
	Atenolol	Atenolol may mask warning signs of hypoglycaemia such as tremor
*	Chloramphenicol	Enhanced effect of glibenclamide
	Chlorpromazine	Possible antagonism of hypoglycaemic effect
	Ciprofloxacin	Possibly enhanced effect of glibenclamide
	Contraceptives, Oral	Antagonism of hypoglycaemic effect by estrogens and progestogens
	Dexamethasone	Antagonism of hypoglycaemic effect
	Enalapril	Hypoglycaemic effect possibly enhanced
*	Fluconazole	Plasma concentration of glibenclamide increased
	Fluphenazine	Possible antagonism of hypoglycaemic effect
	Furosemide	Antagonism of hypoglycaemic effect
	Hydrochlorothiazide	Antagonism of hypoglycaemic effect
	Hydrocortisone	Antagonism of hypoglycaemic effect
*	Ibuprofen	Possibly enhanced effect of glibenclamide
	Levonorgestrel	Antagonism of hypoglycaemic effect
	Medroxyprogesterone	Antagonism of hypoglycaemic effect
	Norethisterone	Antagonism of hypoglycaemic effect
	Prednisolone	Antagonism of hypoglycaemic effect
	Propranolol	Propranolol may mask warning signs of hypoglycaemia such as tremor
*	Rifampicin	Possibly accelerated metabolism (reduced effect) of glibenclamide
	Silver sulfadiazine	Effect of glibenclamide rarely enhanced
	Sulfadiazine	Effect of glibenclamide rarely enhanced
	Sulfadoxine + pyrimethamine	Effect of glibenclamide rarely enhanced
	Sulfamethoxazole + trimethoprim	Effect of glibenclamide rarely enhanced
	Testosterone	Hypoglycaemic effect possibly enhanced
	Timolol	Timolol may mask warning signs of hypoglycaemia such as tremor
	Trimethoprim	Effects of glibenclamide rarely enhanced
*	Warfarin	Possibly enhanced hypoglycaemic effect and changes to anticoagulant effect
Glyceryl trinitrate		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amitriptyline	Reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Atropine	Possibly reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)

	Biperiden	Possibly reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Chlorpromazine	Enhanced hypotensive effect
	Clomipramine	Reduced effect of sublingual glyceryl trinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect
	Enalapril	Enhanced hypotensive effect
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
*	Heparin	Anticoagulant effect reduced by infusion of glyceryl trinitrate
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of hypotensive effect
	Ibuprofen	Antagonism of hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
	Prednisolone	Antagonism of hypotensive effect
	Propranolol	Enhanced hypotensive effect
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect
Grapefruit juice		
	Artemether + lumefantrine	Metabolism of artemether and lumefantrine may be inhibited (manufacturer advises avoid concomitant use)
*	Ciclosporin	Increased plasma ciclosporin concentration (risk of toxicity)
	Efavirenz	Plasma concentration of efavirenz possibly increased
	Nifedipine	Increased plasma nifedipine concentration
*	Simvastatin	Significantly increased plasma simvastatin concentration
	Verapamil	Increased plasma verapamil concentration
Griseofulvin		
	Alcohol	Possibly enhanced effects of alcohol
	Ciclosporin	Plasma ciclosporin concentration possibly reduced
*	Contraceptives, Oral	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
*	Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
*	Medroxyprogesterone	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
*	Norethisterone	Accelerated metabolism of norethisterone (reduced contraceptive effect)
	Phenobarbital	Reduced absorption of griseofulvin (reduced effect)
*	Warfarin	Reduced anticoagulant effect

Haloperidol		
	Alcohol	Enhanced sedative effect
*	Amitriptyline	Increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias
	Amlodipine	Enhanced hypotensive effect
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Atropine	Possibly reduced effects of haloperidol
	Biperiden	Possibly reduced effects of haloperidol
*	Carbamazepine	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
*	Clomipramine	Increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias
	Codeine	Enhanced sedative and hypotensive effect
	Diazepam	Enhanced sedative effect
	Dopamine	Antagonism of hypertensive effect
	Enalapril	Enhanced hypotensive effect
	Ephedrine	Antagonism of hypertensive effect
	Epinephrine	Antagonism of hypertensive effect
*	Ethosuximide	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Fluoxetine	Plasma concentration of haloperidol increased
*	Halothane	Enhanced hypotensive effect
*	Ketamine	Enhanced hypotensive effect
	Levodopa	Antagonism of effects of levodopa
	Lithium	Increased risk of extrapyramidal effects and possibility of neurotoxicity
	Methadone	Enhanced hypotensive and sedative effects
	Methyldopa	Enhanced hypotensive effect; increased risk of extrapyramidal effects
	Metoclopramide	Increased risk of extrapyramidal effects
	Morphine	Enhanced hypotensive and sedative effects
	Nifedipine	Enhanced hypotensive effect
*	Nitrous oxide	Enhanced hypotensive effect
*	Phenobarbital	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
*	Phenytoin	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Procainamide	Increased risk of ventricular arrhythmias
*	Quinidine	Increased risk of ventricular arrhythmias
*	Rifampicin	Accelerated metabolism of haloperidol (reduced plasma haloperidol concentration)
*	Ritonavir	Plasma concentration possibly increased by ritonavir
*	Thiopental	Enhanced hypotensive effect
*	Valproic acid	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Verapamil	Enhanced hypotensive effect
Halothane		
	Acetazolamide	Enhanced hypotensive effect
	Alcuronium	Effects of alcuronium enhanced
	Amiloride	Enhanced hypotensive effect
	Amitriptyline	Increased risk of arrhythmias and hypotension

	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
*	Chlorpromazine	Enhanced hypotensive effect
	Clomipramine	Increased risk of arrhythmias and hypotension
	Diazepam	Enhanced sedative effect
	Enalapril	Enhanced hypotensive effect
*	Epinephrine	Risk of arrhythmias
	Ergometrine	Reduced effect of ergometrine on parturient uterus
*	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
*	Haloperidol	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Isoniazid	Possible potentiation of isoniazid hepatotoxicity
	Isosorbide dinitrate	Enhanced hypotensive effect
*	Levodopa	Risk of arrhythmias
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Oxytocin	Oxytocic effect possibly reduced; enhanced hypotensive effect and risk of arrhythmias
	Propranolol	Enhanced hypotensive effect
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Suxamethonium	Enhanced effects of suxamethonium
	Timolol	Enhanced hypotensive effect
	Vancomycin	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
	Vecuronium	Enhanced effects of vecuronium
*	Verapamil	Enhanced hypotensive effect and AV delay
Heparin		
*	Acetylsalicylic acid	Enhanced anticoagulant effect of heparin
	Enalapril	Increased risk of hyperkalaemia
*	Glyceryl trinitrate	Anticoagulant effect reduced by infusion of glyceryl trinitrate
	Ibuprofen	Possibly increased risk of bleeding
Hydralazine		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Chlorpromazine	Enhanced hypotensive effect
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect
	Enalapril	Enhanced hypotensive effect
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect

	Hydrocortisone	Antagonism of hypotensive effect
	Ibuprofen	Antagonism of hypotensive effect
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
	Prednisolone	Antagonism of hypotensive effect
	Propranolol	Enhanced hypotensive effect
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect
Hydrochlorothiazide		
	Acetazolamide	Increased risk of hypokalaemia
	Alcohol	Enhanced hypotensive effect
	Allopurinol	Increased risk of hypersensitivity, especially in renal impairment
	Amitriptyline	Increased risk of postural hypotension
	Amlodipine	Enhanced hypotensive effect
	Amphotericin B	Increased risk of hypokalaemia
	Atenolol	Enhanced hypotensive effect
	Calcium salts	Increased risk of hypercalcaemia
	Carbamazepine	Increased risk of hyponatraemia
	Chlorpromazine	Enhanced hypotensive effect
	Ciclosporin	Increased risk of nephrotoxicity and possibly hypermagnesaemia
	Cisplatin	Increased risk of nephrotoxicity and ototoxicity
	Clomipramine	Increased risk of postural hypotension
	Contraceptives, Oral	Antagonism of diuretic effect by estrogens
	Dexamethasone	Antagonism of diuretic effect; increased risk of hypokalaemia
	Diazepam	Enhanced hypotensive effect
*	Digoxin	Hypokalaemia caused by hydrochlorothiazide increases cardiac toxicity of digoxin
*	Enalapril	Enhanced hypotensive effect
	Ergocalciferol	Increased risk of hypercalcaemia
	Fluconazole	Plasma concentration of fluconazole increased
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Increased risk of hypokalaemia
	Glibenclamide	Antagonism of hypoglycaemic effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of diuretic effect; increased risk of hypokalaemia
	Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
	Insulins	Antagonism of hypoglycaemic effect
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect

*	Lidocaine	Action of lidocaine antagonized by hypokalaemia caused by hydrochlorothiazide (interaction less likely when lidocaine used topically)
*	Lithium	Reduced lithium excretion (increased plasma lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide
	Metformin	Antagonism of hypoglycaemic effect
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
	Prednisolone	Antagonism of diuretic effect; increased risk of hypokalaemia
	Propranolol	Enhanced hypotensive effect
*	Quinidine	Cardiac toxicity of quinidine increased by hypokalaemia caused by hydrochlorothiazide
	Salbutamol	Increased risk of hypokalaemia with high doses of salbutamol
	Sodium nitroprusside	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect

Hydrocortisone

NOTE. Interactions do not generally apply to hydrocortisone used for topical application.

	Acetazolamide	Increased risk of hypokalaemia; antagonism of diuretic effect
	Acetylsalicylic acid	Increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma salicylate concentration
	Amiloride	Antagonism of diuretic effect
	Amlodipine	Antagonism of hypotensive effect
*	Amphotericin B	Increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions)
	Atenolol	Antagonism of hypotensive effect
	Calcium salts	Reduced absorption of calcium salts
*	Carbamazepine	Accelerated metabolism of hydrocortisone (reduced effect)
	Contraceptives, Oral	Oral contraceptives containing estrogens increase plasma concentration of hydrocortisone
	Digoxin	Increased risk of hypokalaemia
	Enalapril	Antagonism of hypotensive effect
	Erythromycin	Erythromycin possibly inhibits metabolism of hydrocortisone
	Furosemide	Antagonism of diuretic effect; increased risk of hypokalaemia
	Glibenclamide	Antagonism of hypoglycaemic effect
	Glyceryl trinitrate	Antagonism of hypotensive effect
	Hydralazine	Antagonism of hypotensive effect
	Hydrochlorothiazide	Antagonism of diuretic effect; increased risk of hypokalaemia
	Ibuprofen	Increased risk of gastrointestinal bleeding and ulceration
	Insulins	Antagonism of hypoglycaemic effect
	Isosorbide dinitrate	Antagonism of hypotensive effect
	Metformin	Antagonism of hypoglycaemic effect
*	Methotrexate	Increased risk of haematological toxicity

	Methyldopa	Antagonism of hypotensive effect
	Mifepristone	Possibly reduced effects of hydrocortisone for 3–4 days
	Nifedipine	Antagonism of hypotensive effect
*	Phenobarbital	Metabolism of hydrocortisone accelerated (reduced effect)
*	Phenytoin	Metabolism of hydrocortisone accelerated (reduced effect)
	Propranolol	Antagonism of hypotensive effect
*	Rifampicin	Accelerated metabolism of hydrocortisone (reduced effect)
	Ritonavir	Plasma concentration possibly increased by ritonavir
	Salbutamol	Increased risk of hypokalaemia if high doses of salbutamol given with hydrocortisone
	Sodium nitroprusside	Antagonism of hypotensive effect
	Spironolactone	Antagonism of diuretic effect
	Vaccine, Influenza	High doses of hydrocortisone impair immune response
*	Vaccine, Live	High doses of hydrocortisone impair immune response; avoid use of live vaccines with hydrocortisone
	Verapamil	Antagonism of hypotensive effect
*	Warfarin	Anticoagulant effect possibly enhanced or reduced (high-dose hydrocortisone enhances anticoagulant effect)
Hydroxocobalamin		
	Chloramphenicol	Response to hydroxocobalamin reduced
Ibuprofen		
	Acetazolamide	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
*	Acetylsalicylic acid	Avoid concomitant use (increased adverse effects); antiplatelet effect of acetylsalicylic acid possibly reduced
	Amiloride	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia
	Amlodipine	Antagonism of hypotensive effect
	Atenolol	Antagonism of hypotensive effect
*	Ciclosporin	Increased risk of nephrotoxicity
*	Ciprofloxacin	Possibly increased risk of convulsions
	Dexamethasone	Increased risk of gastrointestinal bleeding and ulceration
	Digoxin	Possibly exacerbation of heart failure, reduced renal function, and increased plasma digoxin concentration
	Enalapril	Antagonism of hypotensive effect, increased risk of renal impairment
*	Fluoxetine	Increased risk of bleeding
	Furosemide	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
*	Glibenclamide	Possibly enhanced effect of glibenclamide
	Glyceryl trinitrate	Antagonism of hypotensive effect
	Heparin	Possibly increased risk of bleeding
	Hydralazine	Antagonism of hypotensive effect
	Hydrochlorothiazide	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect
	Hydrocortisone	Increased risk of gastrointestinal bleeding and ulceration
	Isosorbide dinitrate	Antagonism of hypotensive effect
*	Levofloxacin	Possibly increased risk of convulsions
*	Lithium	Reduced excretion of lithium (increased risk of toxicity)
*	Methotrexate	Excretion of methotrexate reduced (increased risk of toxicity)
	Methyldopa	Antagonism of hypotensive effect

	Mifepristone	Avoidance of ibuprofen advised by manufacturer of mifepristone
	Nifedipine	Antagonism of hypotensive effect
*	Ofloxacin	Possibly increased risk of convulsions
	Penicillamine	Possibly increased risk of nephrotoxicity
*	Phenytoin	Effect of phenytoin possibly enhanced
	Prednisolone	Increased risk of gastrointestinal bleeding and ulceration
	Propranolol	Antagonism of hypotensive effect
	Ritonavir	Plasma concentration possibly increased by ritonavir
	Sodium nitroprusside	Antagonism of hypotensive effect
	Spironolactone	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia
	Verapamil	Antagonism of hypotensive effect
*	Warfarin	Anticoagulant effect possibly enhanced
	Zidovudine	Increased risk of haematological toxicity
Imipenem + cilastatin		
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
Immunoglobulin (human), Anti-D		
*	Vaccine, Live	Avoid use of live virus vaccine during *4 weeks before* or during *3 months after* 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 *3 weeks before* or during *3 months after* injection of human normal immunoglobulin (impairment of immune response)
Indinavir		
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Carbamazepine	Possibly reduced plasma indinavir concentration
	Dexamethasone	Possibly reduced plasma indinavir concentration
	Efavirenz	Efavirenz reduces plasma concentration of indinavir
	Nelfinavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
	Nevirapine	Nevirapine reduces plasma concentration of indinavir
*	Phenobarbital	Plasma concentration of indinavir possibly reduced
	Phenytoin	Plasma indinavir concentration possibly reduced
*	Rifampicin	Metabolism accelerated by rifampicin (plasma indinavir concentration reduced—avoid concomitant use)
	Ritonavir	Ritonavir increases plasma concentration of indinavir
	Saquinavir	Indinavir increases plasma concentration of saquinavir
*	Simvastatin	Increased risk of myopathy
Insulins		
	Alcohol	Enhanced hypoglycaemic effect
	Atenolol	Enhanced hypoglycaemic effect; atenolol may mask warning signs of hypoglycaemia such as tremor
	Contraceptives, Oral	Antagonism of hypoglycaemic effect by estrogens and progestogens
	Dexamethasone	Antagonism of hypoglycaemic effect
	Enalapril	Hypoglycaemic effect possibly enhanced
	Furosemide	Antagonism of hypoglycaemic effect

	Hydrochlorothiazide	Antagonism of hypoglycaemic effect
	Hydrocortisone	Antagonism of hypoglycaemic effect
	Levonorgestrel	Antagonism of hypoglycaemic effect
	Medroxyprogesterone	Antagonism of hypoglycaemic effect
	Nifedipine	Occasionally impaired glucose tolerance
	Norethisterone	Antagonism of hypoglycaemic effect
	Prednisolone	Antagonism of hypoglycaemic effect
	Propranolol	Enhanced hypoglycaemic effect; propranolol may mask warning signs of hypoglycaemia such as tremor
	Testosterone	Hypoglycaemic effect possibly enhanced
	Timolol	Enhanced hypoglycaemic effect; timolol may mask warning signs of hypoglycaemia such as tremor
Iron		
	see Ferrous salts	
Isoniazid		
	Amitriptyline	Increased plasma concentration of isoniazid
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of isoniazid
*	Carbamazepine	Increased plasma carbamazepine concentration (also isoniazid hepatotoxicity possibly increased)
	Cycloserine	Increased risk of CNS toxicity
	Diazepam	Metabolism of diazepam inhibited
*	Ethosuximide	Metabolism of ethosuximide inhibited (increased plasma ethosuximide concentration and risk of toxicity)
	Halothane	Possible potentiation of isoniazid hepatotoxicity
	Ketamine	Possible potentiation of isoniazid hepatotoxicity
	Nitrous oxide	Possible potentiation of isoniazid hepatotoxicity
	p-Aminosalicylic acid	Increased plasma concentration of isoniazid
*	Phenytoin	Metabolism of phenytoin inhibited (enhanced effect)
	Thiopental	Possible potentiation of isoniazid hepatotoxicity
Isophane insulin		
	see Insulins	
Isosorbide dinitrate		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amitriptyline	Reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Atropine	Possibly reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Biperiden	Possibly reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Chlorpromazine	Enhanced hypotensive effect
	Clomipramine	Reduced effect of sublingual isosorbide dinitrate tablets (failure to dissolve under the tongue owing to dry mouth)
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect

	Enalapril	Enhanced hypotensive effect
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of hypotensive effect
	Ibuprofen	Antagonism of hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
	Prednisolone	Antagonism of hypotensive effect
	Propranolol	Enhanced hypotensive effect
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect
Ketamine		
	Acetazolamide	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amitriptyline	Increased risk of arrhythmias and hypotension
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
*	Chlorpromazine	Enhanced hypotensive effect
	Clomipramine	Increased risk of arrhythmias and hypotension
	Diazepam	Enhanced sedative effect
	Enalapril	Enhanced hypotensive effect
*	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
*	Haloperidol	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Isoniazid	Possible potentiation of isoniazid hepatotoxicity
	Isosorbide dinitrate	Enhanced hypotensive effect
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Propranolol	Enhanced hypotensive effect
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Vancomycin	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
*	Verapamil	Enhanced hypotensive effect and AV delay
Lamivudine		
	Emtricitabine	No information available; manufacturer advises avoid concomitant use
	Sulfamethoxazole + trimethoprim	Plasma concentration of lamivudine increased (avoid concomitant use of high-dose sulfamethoxazole + trimethoprim)

Levamisole		
	Alcohol	Possibility of disulfiram-like reaction
	Phenytoin	Plasma phenytoin concentration possibly increased
*	Warfarin	Anticoagulant effect possibly enhanced
Levodopa + carbidopa		
	Acetazolamide	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Atropine	Absorption of levodopa possibly reduced
	Biperiden	Absorption of levodopa possibly reduced
	Chlorpromazine	Antagonism of effects of levodopa
	Diazepam	Possibly antagonism of levodopa effects
	Enalapril	Enhanced hypotensive effect
	Ferrous salts	Absorption of levodopa may be reduced by oral ferrous salts
	Fluphenazine	Antagonism of effects of levodopa
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Haloperidol	Antagonism of effects of levodopa
*	Halothane	Risk of arrhythmias
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Isosorbide dinitrate	Enhanced hypotensive effect
	Methyldopa	Enhanced hypotensive effect; antagonism of antiparkinsonism effect
	Nifedipine	Enhanced hypotensive effect
	Phenytoin	Possibly reduced effects of levodopa
	Propranolol	Enhanced hypotensive effect
	Pyridoxine	Antagonism of effects of levodopa unless carbidopa also given
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect
Levofloxacin		
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of levofloxacin
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Ciclosporin	Increased risk of nephrotoxicity
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Ferrous salts	Absorption of levofloxacin reduced by oral ferrous salts
*	Ibuprofen	Possibly increased risk of convulsions
	Warfarin	Possibly enhanced anticoagulant effect
	Zinc sulfate	Reduced absorption of levofloxacin
Levonorgestrel		
	see also Contraceptives, Oral	
*	Carbamazepine	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)

*	Ciclosporin	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
	Glibenclamide	Antagonism of hypoglycaemic effect
*	Griseofulvin	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
	Insulins	Antagonism of hypoglycaemic effect
	Metformin	Antagonism of hypoglycaemic effect
	Nelfinavir	Contraceptive effect of levonorgestrel possibly reduced
*	Nevirapine	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
*	Phenobarbital	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
*	Phenytoin	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
*	Rifampicin	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
*	Ritonavir	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
*	Warfarin	Antagonism of anticoagulant effect
Levothyroxine		
	Amitriptyline	Enhanced effects of amitriptyline
	Calcium salts	Reduced absorption of levothyroxine
	Carbamazepine	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
	Clomipramine	Possibly enhanced effects of clomipramine
	Ferrous salts	Absorption of levothyroxine reduced by oral ferrous salts (give at least 2 hours apart)
	Phenobarbital	Metabolism of levothyroxine accelerated (may increase levothyroxine requirements in hypothyroidism)
	Phenytoin	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism); plasma concentration of phenytoin possibly increased
	Rifampicin	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
*	Warfarin	Enhanced anticoagulant effect
Lidocaine		
	NOTE. Interactions less likely when lidocaine is used topically.	
*	Acetazolamide	Hypokalaemia caused by acetazolamide antagonizes action of lidocaine
*	Atenolol	Increased myocardial depression
	Bupivacaine	Increased myocardial depression
*	Furosemide	Action of lidocaine antagonized by hypokalaemia caused by furosemide
*	Hydrochlorothiazide	Action of lidocaine antagonized by hypokalaemia caused by hydrochlorothiazide
	Lopinavir	Possibly increased plasma concentration of lidocaine
*	Procainamide	Increased myocardial depression
*	Propranolol	Increased myocardial depression; increased risk of lidocaine toxicity
*	Quinidine	Increased myocardial depression
	Suxamethonium	Neuromuscular blockade enhanced and prolonged
*	Timolol	Increased myocardial depression

*	Verapamil	Increased risk of myocardial depression
Lidocaine + epinephrine		
	see Lidocaine; (and epinephrine)	
Lithium		
*	Acetazolamide	Excretion of lithium increased
	Alcuronium	Enhanced muscle relaxant effect
*	Amiloride	Reduced lithium excretion (increased plasma lithium concentration and risk of toxicity)
	Amitriptyline	Risk of toxicity
	Carbamazepine	Neurotoxicity may occur without increased plasma lithium concentration
	Chlorpromazine	Increased risk of extrapyramidal effects and possibility of neurotoxicity
	Clomipramine	Risk of toxicity
*	Enalapril	Enalapril reduces excretion of lithium (increased plasma lithium concentration)
*	Fluoxetine	Increased risk of CNS effects (lithium toxicity reported)
	Fluphenazine	Increased risk of extrapyramidal effects and possibility of neurotoxicity
*	Furosemide	Reduced lithium excretion (increased plasma lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide
	Haloperidol	Increased risk of extrapyramidal effects and possibility of neurotoxicity
*	Hydrochlorothiazide	Reduced lithium excretion (increased plasma lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide
*	Ibuprofen	Reduced excretion of lithium (increased risk of toxicity)
*	Methyldopa	Neurotoxicity may occur without increased plasma lithium concentration
	Metronidazole	Increased lithium toxicity reported
	Neostigmine	Antagonism of effect of neostigmine
	Phenytoin	Neurotoxicity may occur without increased plasma lithium concentration
	Pyridostigmine	Antagonism of effect of pyridostigmine
	Sodium hydrogen carbonate	Increased excretion of lithium (reduced plasma lithium concentration)
*	Spironolactone	Reduced lithium excretion (increased plasma lithium concentration and risk of toxicity)
	Suxamethonium	Enhanced muscle relaxant effect
	Vecuronium	Enhanced muscle relaxant effect
	Verapamil	Neurotoxicity may occur without increased plasma lithium concentration
Lopinavir		
	NOTE. In combination with ritonavir *see also* Ritonavir.	
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Carbamazepine	Possibly reduced plasma lopinavir concentration
	Chlorphenamine	Possibly increased plasma concentration of chlorphenamine
*	Dexamethasone	Possibly reduced plasma lopinavir concentration
*	Efavirenz	Plasma concentration of lopinavir reduced
	Lidocaine	Possibly increased plasma concentration of lidocaine

	Nelfinavir	Plasma concentration of lopinavir reduced; plasma concentration of active metabolite of nelfinavir increased
	Nevirapine	Plasma concentration of lopinavir possibly reduced
*	Phenobarbital	Plasma concentration of lopinavir possibly reduced
	Phenytoin	Plasma lopinavir concentration possibly reduced
*	Rifampicin	Reduced plasma concentration of lopinavir (avoid concomitant use)
	Saquinavir	Increased plasma concentration of saquinavir
*	Simvastatin	Increased risk of myopathy
*	Tenofovir	Plasma concentration of tenofovir increased
Magnesium hydroxide		
	see Antacids	
Magnesium (parenteral)		
	Alcuronium	Enhanced muscle relaxant effect
*	Nifedipine	Profound hypotension reported with nifedipine and intravenous magnesium sulfate in pre-eclampsia
	Suxamethonium	Enhanced muscle relaxant effect
	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)
	Phenobarbital	Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection)
	Phenytoin	Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection)
Medroxyprogesterone acetate		
*	Carbamazepine	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
*	Ciclosporin	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
	Glibenclamide	Antagonism of hypoglycaemic effect
*	Griseofulvin	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception)
	Insulins	Antagonism of hypoglycaemic effect
	Metformin	Antagonism of hypoglycaemic effect
*	Nevirapine	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
*	Phenobarbital	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
*	Phenytoin	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
*	Rifampicin	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)

*	Ritonavir	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
*	Warfarin	Antagonism of anticoagulant effect
Mefloquine		
	Amlodipine	Possibly increased risk of bradycardia
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Atenolol	Increased risk of bradycardia
*	Carbamazepine	Antagonism of anticonvulsant effect
*	Chloroquine	Increased risk of convulsions
	Digoxin	Possibly increased risk of bradycardia
*	Ethosuximide	Antagonism of anticonvulsant effect
	Nifedipine	Possibly increased risk of bradycardia
*	Phenytoin	Antagonism of anticonvulsant effect
	Propranolol	Increased risk of bradycardia
*	Quinidine	Increased risk of ventricular arrhythmias
*	Quinine	Increased risk of convulsions, but should not prevent the use of intravenous quinine in severe cases
	Timolol	Increased risk of bradycardia
*	Valproic acid	Antagonism of anticonvulsant effect
	Verapamil	Possibly increased risk of bradycardia
Mercaptopurine		
*	Allopurinol	Effects of mercaptopurine enhanced and toxicity increased; reduce dose of mercaptopurine
	Phenytoin	Possibly reduced absorption of phenytoin
*	Sulfamethoxazole + trimethoprim	Increased risk of haematological toxicity
	Sulfasalazine	Possibly increased risk of leukopenia
*	Trimethoprim	Increased risk of haematological toxicity
	Vaccine, Live	Avoid use of live vaccines with mercaptopurine (impairment of immune response)
*	Warfarin	Anticoagulant effect possibly reduced
Metformin		
	Alcohol	Enhanced hypoglycaemic effect; increased risk of lactic acidosis
	Atenolol	Atenolol may mask warning signs of hypoglycaemia such as tremor
	Contraceptives, Oral	Antagonism of hypoglycaemic effect by estrogens and progestogens
	Dexamethasone	Antagonism of hypoglycaemic effect
	Enalapril	Hypoglycaemic effect possibly enhanced
	Furosemide	Antagonism of hypoglycaemic effect
	Hydrochlorothiazide	Antagonism of hypoglycaemic effect
	Hydrocortisone	Antagonism of hypoglycaemic effect
	Levonorgestrel	Antagonism of hypoglycaemic effect
	Medroxyprogesterone	Antagonism of hypoglycaemic effect
	Norethisterone	Antagonism of hypoglycaemic effect
	Prednisolone	Antagonism of hypoglycaemic effect
	Propranolol	Propranolol may mask warning signs of hypoglycaemia such as tremor
	Testosterone	Hypoglycaemic effect possibly enhanced

	Timolol	Timolol may mask warning signs of hypoglycaemia such as tremor
Methadone		
	Abacavir	Plasma concentration of methadone possibly reduced
	Alcohol	Enhanced hypotensive and sedative effects
	Amitriptyline	Sedative effects possibly increased
	Carbamazepine	Reduced plasma concentration of methadone
	Chlorpromazine	Enhanced hypotensive and sedative effects
	Clomipramine	Sedative effects possibly increased
	Diazepam	Increased sedative effect
	Efavirenz	Reduced plasma concentration of methadone
	Fluphenazine	Enhanced hypotensive and sedative effects
	Haloperidol	Enhanced hypotensive and sedative effects
	Metoclopramide	Antagonism of effects of metoclopramide on gastrointestinal activity
	Nelfinavir	Reduced plasma concentration of methadone
	Nevirapine	Possibly reduced plasma concentration of methadone
	Phenytoin	Accelerated metabolism of methadone (reduced effect and risk of withdrawal symptoms)
	Rifampicin	Accelerated metabolism of methadone (reduced effect)
	Ritonavir	Reduced plasma concentration of methadone
	Zidovudine	Possibly increased plasma concentration of zidovudine
Methotrexate		
*	Acetylsalicylic acid	Reduced excretion of methotrexate (increased risk of toxicity)
	Amoxicillin	Reduced excretion of methotrexate (increased risk of toxicity)
	Ampicillin	Reduced excretion of methotrexate (increased risk of toxicity)
	Benzylpenicillin	Reduced excretion of methotrexate (increased risk of toxicity)
*	Ciclosporin	Increased toxicity
*	Cisplatin	Risk of pulmonary toxicity
*	Dexamethasone	Increased risk of haematological toxicity
	Doxycycline	Increased risk of methotrexate toxicity
*	Hydrocortisone	Increased risk of haematological toxicity
*	Ibuprofen	Excretion of methotrexate reduced (increased risk of toxicity)
*	Nitrous oxide	Increased antifolate effect (avoid concomitant use)
	Phenoxymethylpenicillin	Reduced excretion of methotrexate (increased risk of toxicity)
	Phenytoin	Reduced absorption of phenytoin; antifolate effect of methotrexate increased
*	Prednisolone	Increased risk of haematological toxicity
*	Pyrimethamine	Antifolate effect of methotrexate increased
	Silver sulfadiazine	Increased risk of methotrexate toxicity
	Sulfadiazine	Risk of methotrexate toxicity increased
*	Sulfadoxine + pyrimethamine	Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased
*	Sulfamethoxazole + trimethoprim	Antifolate effect of methotrexate increased (avoid concomitant use); risk of methotrexate toxicity increased
*	Trimethoprim	Antifolate effect of methotrexate increased (avoid concomitant use)

	Vaccine, Live	Avoid use of live vaccines with methotrexate (impairment of immune response)
Methyldopa		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Chlorpromazine	Enhanced hypotensive effect; increased risk of extrapyramidal effects
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect
	Enalapril	Enhanced hypotensive effect
	Ferrous salts	Oral ferrous salts reduce hypotensive effect of methyldopa
	Fluphenazine	Enhanced hypotensive effect; increased risk of extrapyramidal effects
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Haloperidol	Enhanced hypotensive effect; increased risk of extrapyramidal effects
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of hypotensive effect
	Ibuprofen	Antagonism of hypotensive effect
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect; antagonism of antiparkinsonism effect
*	Lithium	Neurotoxicity may occur without increased plasma lithium concentration
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
	Prednisolone	Antagonism of hypotensive effect
	Propranolol	Enhanced hypotensive effect
*	Salbutamol	Acute hypotension reported with salbutamol infusion
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect
Metoclopramide		
	Acetylsalicylic acid	Enhanced effect of acetylsalicylic acid (increased rate of absorption)
	Atropine	Antagonism of effects of metoclopramide on gastrointestinal activity
	Biperiden	Antagonism of effects of metoclopramide on gastrointestinal activity
	Chlorpromazine	Increased risk of extrapyramidal effects
*	Ciclosporin	Plasma ciclosporin concentration increased
	Codeine	Antagonism of effect of metoclopramide on gastrointestinal activity

	Fluphenazine	Increased risk of extrapyramidal effects
	Haloperidol	Increased risk of extrapyramidal effects
	Methadone	Antagonism of effects of metoclopramide on gastrointestinal activity
	Morphine	Antagonism of effect of metoclopramide on gastrointestinal activity
	Paracetamol	Increased absorption of paracetamol
	Suxamethonium	Enhanced effects of suxamethonium
Metronidazole		
	Alcohol	Disulfiram-like reaction
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Fluorouracil	Metabolism of fluorouracil inhibited (increased toxicity)
	Lithium	Increased lithium toxicity reported
	Phenobarbital	Metabolism of metronidazole accelerated (reduced plasma concentration)
*	Phenytoin	Metabolism of phenytoin inhibited (increased plasma phenytoin concentration)
*	Warfarin	Enhanced anticoagulant effect
Miconazole		
	Amphotericin B	Possibly antagonism of effects of amphotericin B
	Carbamazepine	Plasma concentration of carbamazepine possibly increased
*	Warfarin	Enhanced anticoagulant effect
Mifepristone		
	Acetylsalicylic acid	Manufacturer of mifepristone advises avoid concomitant use
	Beclomethasone	Possibly reduced effects of inhaled beclomethasone for 3–4 days
	Dexamethasone	Possibly reduced effects of dexamethasone for 3–4 days
	Hydrocortisone	Possibly reduced effects of hydrocortisone for 3–4 days
	Ibuprofen	Avoidance of ibuprofen advised by manufacturer of mifepristone
	Prednisolone	Possibly reduced effects of prednisolone for 3–4 days
MMR vaccine		
	see Vaccine, Live	
Morphine		
	Alcohol	Enhanced sedative and hypotensive effects
	Amitriptyline	Possibly increased sedation
	Chlorpromazine	Enhanced sedative and hypotensive effects
	Ciprofloxacin	Manufacturer of ciprofloxacin advises avoid premedication with morphine (reduced plasma ciprofloxacin concentration) when ciprofloxacin used for surgical prophylaxis
	Clomipramine	Possibly increased sedation
	Diazepam	Enhanced sedative effect
	Fluphenazine	Enhanced sedative and hypotensive effects
	Haloperidol	Enhanced sedative and hypotensive effects
	Metoclopramide	Antagonism of effect of metoclopramide on gastrointestinal activity
*	Ritonavir	Ritonavir possibly increases plasma concentration of morphine

Nelfinavir		
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Carbamazepine	Possibly reduced plasma nelfinavir concentration
*	Ciclosporin	Possibly increased plasma ciclosporin concentration
*	Contraceptives, Oral	Accelerated metabolism of estrogens (reduced contraceptive effect); nelfinavir possibly reduces contraceptive effect of progestogens
	Indinavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
	Levonorgestrel	Contraceptive effect of levonorgestrel possibly reduced
	Lopinavir	Plasma concentration of lopinavir reduced; plasma concentration of active metabolite of nelfinavir increased
	Methadone	Reduced plasma concentration of methadone
*	Norethisterone	Possibly reduced contraceptive effect
*	Phenobarbital	Plasma concentration of nelfinavir possibly reduced
	Phenytoin	Reduced plasma phenytoin concentration
*	Quinidine	Increased risk of ventricular arrhythmias (avoid concomitant use)
*	Rifampicin	Plasma concentration of nelfinavir significantly reduced (avoid concomitant use)
	Ritonavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
	Saquinavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
*	Simvastatin	Increased risk of myopathy
Neostigmine		
	Alcuronium	Antagonism of muscle relaxant effect
*	Amikacin	Antagonism of effect of neostigmine
	Atropine	Antagonism of effect of neostigmine
	Biperiden	Antagonism of effect of neostigmine
	Chloroquine	Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine
	Clindamycin	Antagonism of effect of neostigmine
*	Gentamicin	Antagonism of effect of neostigmine
	Lithium	Antagonism of effect of neostigmine
*	Paromomycin	Possibly antagonism
	Procainamide	Antagonism of effect of neostigmine
	Propranolol	Antagonism of effect of neostigmine
	Quinidine	Antagonism of effect of neostigmine
*	Streptomycin	Antagonism of effect of neostigmine
	Suxamethonium	Effect of suxamethonium enhanced
	Vecuronium	Antagonism of muscle relaxant effect
Nevirapine		
*	Contraceptives, Oral	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
	Efavirenz	Plasma efavirenz concentration reduced
*	Fluconazole	Increased plasma concentration of nevirapine
	Indinavir	Nevirapine reduces plasma concentration of indinavir
*	Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
	Lopinavir	Plasma concentration of lopinavir possibly reduced

*	Medroxyprogesterone	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
	Methadone	Possibly reduced plasma concentration of methadone
*	Norethisterone	Accelerated metabolism of norethisterone (reduced contraceptive effect)
*	Rifampicin	Reduced plasma concentration of nevirapine (avoid concomitant use)
	Saquinavir	Plasma concentration of saquinavir reduced
*	Warfarin	Enhanced or reduced anticoagulant effect
Nifedipine		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect
	Alcuronium	Enhanced muscle relaxant effect
	Amiloride	Enhanced hypotensive effect
*	Atenolol	Enhanced hypotensive effect; possibly severe hypotension and heart failure
	Carbamazepine	Probably reduced effect of nifedipine
	Chlorpromazine	Enhanced hypotensive effect
	Ciclosporin	Possibly increased plasma nifedipine concentration (increased risk of adverse effects such as gingival hyperplasia)
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect
*	Digoxin	Possibly increased plasma concentration of digoxin
	Enalapril	Enhanced hypotensive effect
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Grapefruit juice	Increased plasma nifedipine concentration
	Haloperidol	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of hypotensive effect
	Ibuprofen	Antagonism of hypotensive effect
	Insulins	Occasionally impaired glucose tolerance
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
*	Magnesium (parenteral)	Profound hypotension reported with nifedipine and intravenous magnesium sulfate in pre-eclampsia
	Mefloquine	Possibly increased risk of bradycardia
	Methyldopa	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
*	Phenobarbital	Effect of nifedipine probably reduced
*	Phenytoin	Probably reduced effect of nifedipine
	Prednisolone	Antagonism of hypotensive effect
*	Propranolol	Enhanced hypotensive effect; possibly severe hypotension and heart failure
	Quinidine	Reduced plasma quinidine concentration
*	Rifampicin	Accelerated metabolism of nifedipine (plasma concentration significantly reduced)

*	Ritonavir	Plasma concentration possibly increased by ritonavir
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
*	Timolol	Enhanced hypotensive effect; possibly severe hypotension and heart failure
	Vecuronium	Enhanced muscle relaxant effect
	Vincristine	Possibly reduced metabolism of vincristine
Nitrous oxide		
	Acetazolamide	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amitriptyline	Increased risk of arrhythmias and hypotension
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
*	Chlorpromazine	Enhanced hypotensive effect
	Clomipramine	Increased risk of arrhythmias and hypotension
	Diazepam	Enhanced sedative effect
	Enalapril	Enhanced hypotensive effect
*	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
*	Haloperidol	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Isoniazid	Possible potentiation of isoniazid hepatotoxicity
	Isosorbide dinitrate	Enhanced hypotensive effect
*	Methotrexate	Increased antifolate effect (avoid concomitant use)
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Propranolol	Enhanced hypotensive effect
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Vancomycin	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
*	Verapamil	Enhanced hypotensive effect and AV delay
Norethisterone		
	see also Contraceptives, Oral	
*	Carbamazepine	Accelerated metabolism of norethisterone (reduced contraceptive effect)
*	Ciclosporin	Inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration)
	Glibenclamide	Antagonism of hypoglycaemic effect
*	Griseofulvin	Accelerated metabolism of norethisterone (reduced contraceptive effect)
	Insulins	Antagonism of hypoglycaemic effect
	Metformin	Antagonism of hypoglycaemic effect
*	Nelfinavir	Possibly reduced contraceptive effect
*	Nevirapine	Accelerated metabolism of norethisterone (reduced contraceptive effect)
*	Phenobarbital	Accelerated metabolism of norethisterone (reduced contraceptive effect)

*	Phenytoin	Accelerated metabolism of norethisterone (reduced contraceptive effect)
*	Rifampicin	Accelerated metabolism of norethisterone (reduced contraceptive effect)
*	Ritonavir	Accelerated metabolism of norethisterone (reduced contraceptive effect)
*	Warfarin	Antagonism of anticoagulant effect
Ofloxacin		
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of ofloxacin
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Ciclosporin	Increased risk of nephrotoxicity
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Ferrous salts	Absorption of ofloxacin reduced by oral ferrous salts
*	Ibuprofen	Possibly increased risk of convulsions
*	Warfarin	Enhanced anticoagulant effect
	Zinc sulfate	Reduced absorption of ofloxacin
Oxygen		
*	Bleomycin	Serious pulmonary toxicity in patients exposed to conventional oxygen concentrations during anaesthesia
Oxytocin		
	Ephedrine	Risk of hypertension due to enhanced vasopressor effect of ephedrine
	Epinephrine	Risk of hypertension due to enhanced vasopressor effect of epinephrine
	Halothane	Oxytocic effect possibly reduced; enhanced hypotensive effect and risk of arrhythmias
p-Aminosalicylic acid		
	Isoniazid	Increased plasma concentration of isoniazid
Paracetamol		
	Metoclopramide	Increased absorption of paracetamol
	Warfarin	Prolonged regular use of paracetamol possibly enhances anticoagulant effect
Paromomycin		
	Amphotericin B	Possibly increased risk of nephrotoxicity
	Cisplatin	Increased risk of ototoxicity
	Furosemide	Increased risk of ototoxicity
*	Neostigmine	Possibly antagonism of neostigmine
*	Pyridostigmine	Possibly antagonism of pyridostigmine
*	Suxamethonium	Possibly enhanced effects of suxamethonium
	Vancomycin	Increased risk of ototoxicity
Penicillamine		
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of penicillamine
	Digoxin	Plasma concentration of digoxin possibly reduced
	Ferrous salts	Oral ferrous salts reduce absorption of penicillamine

	Ibuprofen	Possibly increased risk of nephrotoxicity
	Zinc sulfate	Absorption of penicillamine and zinc sulfate reduced
Pentamidine		
	Amphotericin B	Possibly increased risk of nephrotoxicity
Phenobarbital		
	Abacavir	Plasma concentration of abacavir possibly reduced
	Acetazolamide	Increased risk of osteomalacia
	Alcohol	Enhanced sedative effect
*	Amitriptyline	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of amitriptyline possibly accelerated (reduced plasma concentration)
*	Amlodipine	Probably reduced effect of amlodipine
*	Carbamazepine	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of carbamazepine reduced
*	Chloramphenicol	Metabolism of chloramphenicol accelerated (reduced plasma chloramphenicol concentration)
*	Chlorpromazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Ciclosporin	Metabolism of ciclosporin accelerated (reduced effect)
*	Clomipramine	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of clomipramine possibly accelerated (reduced plasma concentration)
*	Contraceptives, Oral	Metabolism of estrogens and progestogens accelerated (reduced contraceptive effect)
*	Dexamethasone	Metabolism of dexamethasone accelerated (reduced effect)
	Doxycycline	Metabolism of doxycycline accelerated (reduced plasma concentration)
	Ergocalciferol	Ergocalciferol requirements possibly increased
	Ethosuximide	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of ethosuximide possibly reduced
	Etoposide	Possibly reduced plasma concentration of etoposide
	Fluoxetine	Antagonism of anticonvulsive effect (convulsive threshold lowered)
*	Fluphenazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Folic acid; folinic acid	Plasma concentration of phenobarbital possibly reduced
	Griseofulvin	Reduced absorption of griseofulvin (reduced effect)
*	Haloperidol	Antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration)
*	Hydrocortisone	Metabolism of hydrocortisone accelerated (reduced effect)
*	Indinavir	Plasma concentration of indinavir possibly reduced
*	Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
	Levothyroxine	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
*	Lopinavir	Plasma concentration of lopinavir possibly reduced
	Mebendazole	Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection)

*	Medroxyprogesterone	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
	Metronidazole	Metabolism of metronidazole accelerated (reduced plasma concentration)
*	Nelfinavir	Plasma concentration of nelfinavir possibly reduced
*	Nifedipine	Effect of nifedipine probably reduced
*	Norethisterone	Accelerated metabolism of norethisterone (reduced contraceptive effect)
	Phenytoin	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of phenobarbital often raised
*	Prednisolone	Metabolism of prednisolone accelerated (reduced effect)
	Quinidine	Metabolism of quinidine accelerated (reduced plasma concentration)
*	Saquinavir	Plasma concentration of saquinavir possibly reduced
	Valproic acid	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid reduced; plasma phenobarbital concentration increased
*	Verapamil	Effect of verapamil probably reduced
*	Warfarin	Metabolism of warfarin accelerated (reduced anticoagulant effect)
Phenoxymethylpenicillin		
	Contraceptives, Oral	Contraceptive effect of estrogens possibly reduced (risk probably small)
	Methotrexate	Reduced excretion of methotrexate (increased risk of toxicity)
Phenytoin		
	Abacavir	Plasma concentration of abacavir possibly reduced
	Acetazolamide	Increased risk of osteomalacia
	Acetylsalicylic acid	Enhancement of effect of phenytoin
	Alcohol	Plasma phenytoin concentration reduced with regular large amounts of alcohol
	Alcuronium	Antagonism of muscle relaxant effect (accelerated recovery from neuromuscular blockade)
*	Amitriptyline	Antagonism of anticonvulsant effect (convulsive threshold lowered); possibly reduced plasma amitriptyline concentration
	Amlodipine	Probably reduced effect of amlodipine
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of phenytoin
	Azathioprine	Possibly reduced absorption of phenytoin
	Bleomycin	Possibly reduced absorption of phenytoin
*	Carbamazepine	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of carbamazepine often lowered
	Chlorambucil	Possibly reduced absorption of phenytoin
*	Chloramphenicol	Plasma phenytoin concentration increased (increased risk of toxicity)
	Chloroquine	Possibly increased risk of convulsions

*	Chlorpromazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Ciclosporin	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
	Ciprofloxacin	Plasma phenytoin concentration can be increased or decreased by ciprofloxacin
	Cisplatin	Reduced absorption of phenytoin
*	Clomipramine	Antagonism of anticonvulsant effect (convulsive threshold lowered); possibly reduced plasma clomipramine concentration
*	Contraceptives, Oral	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
	Cyclophosphamide	Possibly reduced absorption of phenytoin
	Cytarabine	Reduced absorption of phenytoin
	Dacarbazine	Possibly reduced absorption of phenytoin
	Dactinomycin	Possibly reduced absorption of phenytoin
	Daunorubicin	Possibly reduced absorption of phenytoin
*	Dexamethasone	Metabolism of dexamethasone accelerated (reduced effect)
	Diazepam	Plasma phenytoin concentration possibly increased or decreased by diazepam
	Digoxin	Plasma concentration of digoxin possibly reduced
	Doxorubicin	Possibly reduced absorption of phenytoin
	Doxycycline	Increased metabolism of doxycycline (reduced plasma concentration)
	Ergocalciferol	Ergocalciferol requirements possibly increased
*	Ethosuximide	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin possibly increased; plasma concentration of ethosuximide possibly reduced
	Etoposide	Possibly reduced absorption of phenytoin and possibly reduced plasma concentration of etoposide
*	Fluconazole	Plasma concentration of phenytoin increased (consider reducing dose of phenytoin)
	Fluorouracil	Metabolism of phenytoin possibly inhibited (increased risk of toxicity)
*	Fluoxetine	Plasma concentration of phenytoin increased
*	Fluphenazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Folic acid; folinic acid	Plasma phenytoin concentration possibly reduced
*	Haloperidol	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Hydrocortisone	Metabolism of hydrocortisone accelerated (reduced effect)
*	Ibuprofen	Effect of phenytoin possibly enhanced
	Indinavir	Plasma indinavir concentration possibly reduced
*	Isoniazid	Metabolism of phenytoin inhibited (enhanced effect)
	Levamisole	Plasma phenytoin concentration possibly increased
	Levodopa	Possibly reduced effects of levodopa
*	Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
	Levothyroxine	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism); plasma concentration of phenytoin possibly increased
	Lithium	Neurotoxicity may occur without increased plasma lithium concentration

	Lopinavir	Plasma lopinavir concentration possibly reduced
	Mebendazole	Reduced plasma mebendazole concentration (possibly increase mebendazole dose in tissue infection)
*	Medroxyprogesterone	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
*	Mefloquine	Antagonism of anticonvulsant effect
	Mercaptopurine	Possibly reduced absorption of phenytoin
	Methadone	Accelerated metabolism of methadone (reduced effect and risk of withdrawal symptoms)
	Methotrexate	Reduced absorption of phenytoin; antifolate effect of methotrexate increased
*	Metronidazole	Metabolism of phenytoin inhibited (increased plasma phenytoin concentration)
	Nelfinavir	Reduced plasma phenytoin concentration
*	Nifedipine	Probably reduced effect of nifedipine
*	Norethisterone	Accelerated metabolism of norethisterone (reduced contraceptive effect)
	Phenobarbital	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of phenobarbital often raised
	Praziquantel	Plasma praziquantel concentration reduced
*	Prednisolone	Metabolism of prednisolone accelerated (reduced effect)
	Procarbazine	Reduced absorption of phenytoin
*	Pyrimethamine	Antagonism of anticonvulsant effect; increased antifolate effect
*	Quinidine	Accelerated metabolism of quinidine (reduced plasma quinidine concentration)
*	Rifampicin	Accelerated metabolism of phenytoin (reduced plasma concentration)
	Saquinavir	Plasma saquinavir concentration possibly reduced
	Silver sulfadiazine	Possibly increased plasma concentration of phenytoin
	Sulfadiazine	Plasma phenytoin concentration possibly increased
*	Sulfadoxine + pyrimethamine	Plasma phenytoin concentration possibly increased; increased antifolate effect
*	Sulfamethoxazole + trimethoprim	Antifolate effect and plasma phenytoin concentration increased
*	Trimethoprim	Antifolate effect and plasma phenytoin concentration increased
	Vaccine, Influenza	Enhanced effect of phenytoin
	Valproic acid	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid reduced; plasma concentration of phenytoin increased or possibly reduced
	Vecuronium	Antagonism of muscle relaxant effect (accelerated recovery from neuromuscular blockade)
	Verapamil	Reduced effect of verapamil
	Vinblastine	Possibly reduced absorption of phenytoin
	Vincristine	Possibly reduced absorption of phenytoin
*	Warfarin	Accelerated metabolism of warfarin (possibility of reduced anticoagulant effect, but enhancement also reported)
	Zidovudine	Plasma phenytoin concentration increased or decreased by zidovudine

Phytomenadione		
*	Warfarin	Antagonism of anticoagulant effect
Pilocarpine		
	Atenolol	Increased risk of arrhythmias
	Atropine	Antagonism of effects of pilocarpine
	Biperiden	Antagonism of effects of pilocarpine
	Propranolol	Increased risk of arrhythmias
	Timolol	Increased risk of arrhythmias
Poliomyelitis, Vaccine (oral)		
	see Vaccine, Live	
Potassium chloride		
	see Potassium salts	
Potassium salts		
*	Amiloride	Increased risk of hyperkalaemia
*	Ciclosporin	Increased risk of hyperkalaemia
*	Enalapril	Increased risk of severe hyperkalaemia
*	Spironolactone	Risk of hyperkalaemia
Praziquantel		
	Albendazole	Increased plasma concentration of active metabolite of albendazole
	Carbamazepine	Plasma praziquantel concentration reduced
	Chloroquine	Plasma praziquantel concentration possibly reduced
	Dexamethasone	Plasma praziquantel concentration reduced
	Phenytoin	Plasma praziquantel concentration reduced
Prednisolone		
	Acetazolamide	Increased risk of hypokalaemia; antagonism of diuretic effect
	Acetylsalicylic acid	Increased risk of gastrointestinal bleeding and ulceration; prednisolone reduces plasma salicylate concentration
	Amiloride	Antagonism of diuretic effect
	Amlodipine	Antagonism of hypotensive effect
*	Amphotericin B	Increased risk of hypokalaemia (avoid concomitant use unless prednisolone needed to control reactions)
	Atenolol	Antagonism of hypotensive effect
	Calcium salts	Reduced absorption of calcium salts
*	Carbamazepine	Accelerated metabolism of prednisolone (reduced effect)
	Ciclosporin	Increased plasma concentration of prednisolone
	Contraceptives, Oral	Oral contraceptives containing estrogens increase plasma concentration of prednisolone
	Digoxin	Increased risk of hypokalaemia
	Enalapril	Antagonism of hypotensive effect
	Erythromycin	Erythromycin possibly inhibits metabolism of prednisolone
	Furosemide	Antagonism of diuretic effect; increased risk of hypokalaemia
	Glibenclamide	Antagonism of hypoglycaemic effect
	Glyceryl trinitrate	Antagonism of hypotensive effect
	Hydralazine	Antagonism of hypotensive effect
	Hydrochlorothiazide	Antagonism of diuretic effect; increased risk of hypokalaemia
	Ibuprofen	Increased risk of gastrointestinal bleeding and ulceration
	Insulins	Antagonism of hypoglycaemic effect
	Isosorbide dinitrate	Antagonism of hypotensive effect
	Metformin	Antagonism of hypoglycaemic effect

*	Methotrexate	Increased risk of haematological toxicity
	Methyldopa	Antagonism of hypotensive effect
	Mifepristone	Possibly reduced effects of prednisolone for 3–4 days
	Nifedipine	Antagonism of hypotensive effect
*	Phenobarbital	Metabolism of prednisolone accelerated (reduced effect)
*	Phenytoin	Metabolism of prednisolone accelerated (reduced effect)
	Propranolol	Antagonism of hypotensive effect
*	Rifampicin	Accelerated metabolism of prednisolone (reduced effect)
	Ritonavir	Plasma concentration possibly increased by ritonavir
	Salbutamol	Increased risk of hypokalaemia if high doses of salbutamol given with prednisolone
	Sodium nitroprusside	Antagonism of hypotensive effect
	Spironolactone	Antagonism of diuretic effect
	Vaccine, Influenza	High doses of prednisolone impair immune response
*	Vaccine, Live	High doses of prednisolone impair immune response; avoid use of live vaccines with prednisolone
	Verapamil	Antagonism of hypotensive effect
*	Warfarin	Anticoagulant effect possibly enhanced or reduced (high-dose prednisolone enhances anticoagulant effect)
Primaquine		
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
Procainamide		
*	Alcuronium	Enhanced muscle relaxant effect
*	Amitriptyline	Increased risk of ventricular arrhythmias
*	Artemether + lumefantrine	Risk of ventricular arrhythmias; manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Atenolol	Increased myocardial depression
	Bupivacaine	Increased myocardial depression
*	Chlorpromazine	Increased risk of ventricular arrhythmias
*	Clomipramine	Increased risk of ventricular arrhythmias
*	Fluphenazine	Increased risk of ventricular arrhythmias
*	Haloperidol	Increased risk of ventricular arrhythmias
*	Lidocaine	Increased myocardial depression (interaction less likely when lidocaine used topically)
	Neostigmine	Antagonism of effect of neostigmine
*	Propranolol	Increased risk of myocardial depression
	Pyridostigmine	Antagonism of effect of pyridostigmine
*	Quinidine	Increased myocardial depression
	Sulfamethoxazole + trimethoprim	Increased plasma procainamide concentration
*	Suxamethonium	Enhanced muscle relaxant effect
*	Timolol	Increased myocardial depression
	Trimethoprim	Increased plasma procainamide concentration
*	Vecuronium	Enhanced muscle relaxant effect
Procaine benzylpenicillin		
	see Benzylpenicillin	
Procarbazine		
	Alcohol	Disulfiram-like reaction
	Phenytoin	Reduced absorption of phenytoin
	Vaccine, Live	Avoid use of live vaccines with procarbazine (impairment of immune response)

Proguanil		
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Pyrimethamine	Increased antifolate effect
	Warfarin	Isolated reports of enhanced anticoagulant effect
Promethazine		
	Alcohol	Enhanced sedative effect
	Amitriptyline	Increased antimuscarinic and sedative effects
	Atropine	Increased risk of antimuscarinic adverse effects
	Biperiden	Increased risk of antimuscarinic adverse effects
	Clomipramine	Increased antimuscarinic and sedative effects
	Diazepam	Enhanced sedative effect
Propranolol		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect
	Alcuronium	Enhanced muscle relaxant effect
	Amiloride	Enhanced hypotensive effect
	Amlodipine	Enhanced hypotensive effect
*	Bupivacaine	Increased risk of bupivacaine toxicity
*	Chlorpromazine	Concomitant administration may increase plasma concentration of both drugs; enhanced hypotensive effect
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect
	Digoxin	Increased risk of AV block and bradycardia
	Enalapril	Enhanced hypotensive effect
*	Epinephrine	Severe hypertension
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glibenclamide	Propranolol may mask warning signs of hypoglycaemia such as tremor
	Glyceryl trinitrate	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of hypotensive effect
	Ibuprofen	Antagonism of hypotensive effect
	Insulins	Enhanced hypoglycaemic effect; propranolol may mask warning signs of hypoglycaemia such as tremor
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
*	Lidocaine	Increased myocardial depression; increased risk of lidocaine toxicity (interaction less likely when lidocaine used topically)
	Mefloquine	Increased risk of bradycardia
	Metformin	Propranolol may mask warning signs of hypoglycaemia such as tremor
	Methyldopa	Enhanced hypotensive effect
	Neostigmine	Antagonism of effect of neostigmine
*	Nifedipine	Enhanced hypotensive effect; possibly severe hypotension and heart failure
	Nitrous oxide	Enhanced hypotensive effect

	Pilocarpine	Increased risk of arrhythmias
	Prednisolone	Antagonism of hypotensive effect
*	Procainamide	Increased risk of myocardial depression
	Pyridostigmine	Antagonism of effect of pyridostigmine
*	Quinidine	Increased myocardial depression
	Rifampicin	Metabolism of propranolol accelerated (significantly reduced plasma concentration)
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Suxamethonium	Enhanced muscle relaxant effect
	Thiopental	Enhanced hypotensive effect
	Vecuronium	Enhanced muscle relaxant effect
*	Verapamil	Asystole, severe hypotension, and heart failure
Pyridostigmine		
	Alcuronium	Antagonism of muscle relaxant effect
*	Amikacin	Antagonism of effect of pyridostigmine
	Atropine	Antagonism of effect of pyridostigmine
	Biperiden	Antagonism of effect of pyridostigmine
	Chloroquine	Chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of pyridostigmine
	Clindamycin	Antagonism of effect of pyridostigmine
*	Gentamicin	Antagonism of effect of pyridostigmine
	Lithium	Antagonism of effect of pyridostigmine
*	Paromomycin	Possibly antagonism
	Procainamide	Antagonism of effect of pyridostigmine
	Propranolol	Antagonism of effect of pyridostigmine
	Quinidine	Antagonism of effect of pyridostigmine
*	Streptomycin	Antagonism of effect of pyridostigmine
	Suxamethonium	Effect of suxamethonium enhanced
	Vecuronium	Antagonism of muscle relaxant effect
Pyridoxine		
	Levodopa	Antagonism of effects of levodopa unless carbidopa also given
Pyrimethamine		
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Methotrexate	Antifolate effect of methotrexate increased
*	Phenytoin	Antagonism of anticonvulsant effect; increased antifolate effect
	Proguanil	Increased antifolate effect
*	Silver sulfadiazine	Increased antifolate effect
*	Sulfadiazine	Increased antifolate effect
*	Sulfamethoxazole + trimethoprim	Increased antifolate effect
*	Trimethoprim	Increased antifolate effect
	Zidovudine	Increased antifolate effect
Pyrimethamine + sulfadoxine		
	see Sulfadoxine + pyrimethamine	
Quinidine		
*	Acetazolamide	Cardiac toxicity of quinidine increased if hypokalaemia occurs; acetazolamide possibly reduces excretion of quinidine (increased plasma concentration)

*	Alcuronium	Enhanced muscle relaxant effect
*	Amitriptyline	Increased risk of ventricular arrhythmias
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced quinidine excretion in alkaline urine (plasma quinidine concentration occasionally increased)
*	Artemether + lumefantrine	Risk of ventricular arrhythmias; manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Atenolol	Increased myocardial depression
	Bupivacaine	Increased myocardial depression
	Chloroquine	Increased risk of ventricular arrhythmias
*	Chlorpromazine	Increased risk of ventricular arrhythmias
*	Clomipramine	Increased risk of ventricular arrhythmias
*	Digoxin	Plasma concentration of digoxin increased (halve dose of digoxin)
*	Erythromycin	Increased risk of ventricular arrhythmias with parenteral erythromycin
*	Fluphenazine	Increased risk of ventricular arrhythmias
*	Furosemide	Cardiac toxicity of quinidine increased by hypokalaemia caused by furosemide
*	Haloperidol	Increased risk of ventricular arrhythmias
*	Hydrochlorothiazide	Cardiac toxicity of quinidine increased by hypokalaemia caused by hydrochlorothiazide
*	Lidocaine	Increased myocardial depression (interaction less likely when lidocaine used topically)
*	Mefloquine	Increased risk of ventricular arrhythmias
*	Nelfinavir	Increased risk of ventricular arrhythmias (avoid concomitant use)
	Neostigmine	Antagonism of effect of neostigmine
	Nifedipine	Reduced plasma quinidine concentration
	Phenobarbital	Metabolism of quinidine accelerated (reduced plasma concentration)
*	Phenytoin	Accelerated metabolism of quinidine (reduced plasma quinidine concentration)
*	Procainamide	Increased myocardial depression
*	Propranolol	Increased myocardial depression
	Pyridostigmine	Antagonism of effect of pyridostigmine
*	Rifampicin	Accelerated metabolism of quinidine (reduced plasma quinidine concentration)
*	Ritonavir	Increased plasma quinidine concentration (increased risk of ventricular arrhythmias—avoid concomitant use)
*	Suxamethonium	Enhanced muscle relaxant effect
*	Timolol	Increased myocardial depression
*	Vecuronium	Enhanced muscle relaxant effect
*	Verapamil	Increased plasma quinidine concentration (extreme hypotension may occur)
*	Warfarin	Anticoagulant effect may be enhanced
Quinine		
*	Artemether + lumefantrine	Risk of ventricular arrhythmias; manufacturer of artemether + lumefantrine advises avoid concomitant use
	Chloroquine	Increased risk of ventricular arrhythmias
*	Digoxin	Plasma concentration of digoxin increased
*	Mefloquine	Increased risk of convulsions, but should not prevent the use of intravenous quinine in severe cases

	Suxamethonium	Possibly enhanced effects of suxamethonium
Ribavirin		
*	Didanosine	Increased risk of adverse effects; manufacturer of ribavirin advises avoid concomitant use
*	Stavudine	Possibly inhibited effects of stavudine
*	Zidovudine	Possibly inhibited effects of zidovudine
Rifampicin		
	Abacavir	Plasma concentration of abacavir possibly reduced
	Amitriptyline	Plasma concentration of amitriptyline possibly reduced
	Antacids (Aluminium hydroxide; Magnesium hydroxide)	Reduced absorption of rifampicin
	Chloramphenicol	Accelerated metabolism of chloramphenicol (reduced plasma chloramphenicol concentration)
*	Ciclosporin	Accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration)
	Clomipramine	Plasma concentration of clomipramine possibly reduced
*	Contraceptives, Oral	Accelerated metabolism of estrogens and progestogens (reduced contraceptive effect)
	Dapsone	Reduced plasma dapsone concentration
*	Dexamethasone	Accelerated metabolism of dexamethasone (reduced effect)
	Diazepam	Metabolism of diazepam accelerated (reduced plasma concentration)
	Digoxin	Plasma concentration of digoxin possibly reduced
	Doxycycline	Plasma doxycycline concentration possibly reduced
	Efavirenz	Reduced plasma concentration of efavirenz (increase efavirenz dose)
*	Fluconazole	Accelerated metabolism of fluconazole (reduced plasma concentration)
*	Glibenclamide	Possibly accelerated metabolism (reduced effect) of glibenclamide
*	Haloperidol	Accelerated metabolism of haloperidol (reduced plasma haloperidol concentration)
*	Hydrocortisone	Accelerated metabolism of hydrocortisone (reduced effect)
*	Indinavir	Metabolism accelerated by rifampicin (plasma indinavir concentration reduced—avoid concomitant use)
*	Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
	Levothyroxine	Accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism)
*	Lopinavir	Reduced plasma concentration of lopinavir (avoid concomitant use)
*	Medroxyprogesterone	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
	Methadone	Accelerated metabolism of methadone (reduced effect)
*	Nelfinavir	Plasma concentration of nelfinavir significantly reduced (avoid concomitant use)
*	Nevirapine	Reduced plasma concentration of nevirapine (avoid concomitant use)

*	Nifedipine	Accelerated metabolism of nifedipine (plasma concentration significantly reduced)
*	Norethisterone	Accelerated metabolism of norethisterone (reduced contraceptive effect)
*	Phenytoin	Accelerated metabolism of phenytoin (reduced plasma concentration)
*	Prednisolone	Accelerated metabolism of prednisolone (reduced effect)
	Propranolol	Metabolism of propranolol accelerated (significantly reduced plasma concentration)
*	Quinidine	Accelerated metabolism of quinidine (reduced plasma quinidine concentration)
*	Saquinavir	Plasma concentration of saquinavir significantly reduced—avoid concomitant use
*	Verapamil	Accelerated metabolism of verapamil (plasma concentration significantly reduced)
*	Warfarin	Accelerated metabolism of warfarin (reduced anticoagulant effect)
	Zidovudine	Manufacturer of zidovudine advises avoid concomitant use
Ritonavir		
*	Amitriptyline	Plasma concentration possibly increased by ritonavir
*	Amlodipine	Possibly increased plasma concentration of amlodipine
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Azithromycin	Plasma concentration of azithromycin possibly increased
*	Carbamazepine	Plasma concentration possibly increased by ritonavir
*	Chlorpromazine	Plasma concentration possibly increased by ritonavir
*	Ciclosporin	Plasma concentration possibly increased by ritonavir
*	Clomipramine	Plasma concentration possibly increased by ritonavir
*	Codeine	Ritonavir possibly increases plasma concentration of codeine
*	Contraceptives, Oral	Accelerated metabolism of estrogens (reduced contraceptive effect)
	Dexamethasone	Plasma concentration possibly increased by ritonavir
*	Diazepam	Plasma concentration possibly increased by ritonavir (risk of extreme sedation and respiratory depression—avoid concomitant use)
	Efavirenz	Increased risk of toxicity (monitor liver function tests)
	Erythromycin	Plasma concentration possibly increased by ritonavir
	Fluconazole	Plasma concentration of fluconazole increased by ritonavir
*	Fluoxetine	Plasma concentration possibly increased by ritonavir
*	Fluphenazine	Plasma concentration possibly increased by ritonavir
*	Haloperidol	Plasma concentration possibly increased by ritonavir
	Hydrocortisone	Plasma concentration possibly increased by ritonavir
	Ibuprofen	Plasma concentration possibly increased by ritonavir
	Indinavir	Ritonavir increases plasma concentration of indinavir
*	Levonorgestrel	Accelerated metabolism of levonorgestrel (reduced contraceptive effect)
*	Medroxyprogesterone	Accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate used for contraception)
	Methadone	Reduced plasma concentration of methadone
*	Morphine	Ritonavir possibly increases plasma concentration of morphine

	Nelfinavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
*	Nifedipine	Plasma concentration possibly increased by ritonavir
*	Norethisterone	Accelerated metabolism of norethisterone (reduced contraceptive effect)
	Prednisolone	Plasma concentration possibly increased by ritonavir
*	Quinidine	Increased plasma quinidine concentration (increased risk of ventricular arrhythmias—avoid concomitant use)
	Saquinavir	Ritonavir increases plasma concentration of saquinavir
*	Simvastatin	Increased risk of myopathy
*	Verapamil	Plasma concentration possibly increased by ritonavir
*	Warfarin	Plasma concentration possibly increased by ritonavir
Rotavirus vaccine		
	see Vaccine, live	
Rubella vaccine		
	see Vaccine, live	
Salbutamol		
	Acetazolamide	Increased risk of hypokalaemia with high doses of salbutamol
	Dexamethasone	Increased risk of hypokalaemia if high doses of salbutamol given with dexamethasone
	Digoxin	Possibly reduced plasma concentration of digoxin
	Furosemide	Increased risk of hypokalaemia with high doses of salbutamol
	Hydrochlorothiazide	Increased risk of hypokalaemia with high doses of salbutamol
	Hydrocortisone	Increased risk of hypokalaemia if high doses of salbutamol given with hydrocortisone
*	Methyldopa	Acute hypotension reported with salbutamol infusion
	Prednisolone	Increased risk of hypokalaemia if high doses of salbutamol given with prednisolone
Saquinavir		
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
	Carbamazepine	Possibly reduced plasma saquinavir concentration
*	Ciclosporin	Plasma concentration of both ciclosporin and saquinavir increased
	Dexamethasone	Possibly reduced plasma saquinavir concentration
	Efavirenz	Efavirenz significantly reduces plasma concentration of saquinavir
	Fluconazole	Plasma concentration of saquinavir possibly increased
	Indinavir	Indinavir increases plasma concentration of saquinavir
	Lopinavir	Increased plasma concentration of saquinavir
	Nelfinavir	Combination may lead to increased plasma concentration of either drug (or both drugs)
	Nevirapine	Plasma concentration of saquinavir reduced
*	Phenobarbital	Plasma concentration of saquinavir possibly reduced
	Phenytoin	Plasma saquinavir concentration possibly reduced
*	Rifampicin	Plasma concentration of saquinavir significantly reduced—avoid concomitant use
*	Ritonavir	Ritonavir increases plasma concentration of saquinavir
*	Simvastatin	Increased risk of myopathy
	Warfarin	Possibly enhanced anticoagulant effect

Silver sulfadiazine

NOTE. Interactions may apply when silver sulfadiazine is used to treat large areas of skin.

*	Ciclosporin	Increased risk of nephrotoxicity; possibly reduced plasma concentration of ciclosporin
	Glibenclamide	Effects of glibenclamide rarely enhanced
	Methotrexate	Increased risk of methotrexate toxicity
	Phenytoin	Possibly increased plasma concentration of phenytoin
*	Pyrimethamine	Increased antifolate effect
	Thiopental	Enhanced effects of thiopental
*	Warfarin	Enhanced anticoagulant effect

Simvastatin

*	Ciclosporin	Increased risk of myopathy
*	Clotrimazole	Increased risk of myopathy
*	Erythromycin	Increased risk of myopathy
*	Grapefruit juice	Significantly increased plasma simvastatin concentration
*	Indinavir	Increased risk of myopathy
*	Lopinavir	Increased risk of myopathy
*	Nelfinavir	Increased risk of myopathy
*	Ritonavir	Increased risk of myopathy
*	Saquinavir	Increased risk of myopathy
*	Verapamil	Increased risk of myopathy
*	Warfarin	Enhanced anticoagulant effect

Sodium fluoride

	Calcium salts	Reduced absorption of sodium fluoride

Sodium hydrogen carbonate

	Lithium	Increased excretion of lithium (reduced plasma lithium concentration)

Sodium lactate, compound solution

see Potassium salts; Sodium hydrogen carbonate

Sodium nitroprusside

	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Chlorpromazine	Enhanced hypotensive effect
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect
	Enalapril	Enhanced hypotensive effect
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of hypotensive effect
	Ibuprofen	Antagonism of hypotensive effect
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect

	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
	Prednisolone	Antagonism of hypotensive effect
	Propranolol	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect
Sodium valproate		
	see Valproic acid	
Soluble insulin		
	see Insulins	
Spironolactone		
	Acetylsalicylic acid	Antagonism of diuretic effect
	Alcohol	Enhanced hypotensive effect
	Amitriptyline	Increased risk of postural hypotension
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
	Carbamazepine	Increased risk of hyponatraemia
	Chlorpromazine	Enhanced hypotensive effect
*	Ciclosporin	Increased risk of hyperkalaemia
	Cisplatin	Increased risk of nephrotoxicity and ototoxicity
	Clomipramine	Increased risk of postural hypotension
	Contraceptives, Oral	Antagonism of diuretic effect by estrogens
	Dexamethasone	Antagonism of diuretic effect
	Diazepam	Enhanced hypotensive effect
*	Digoxin	Plasma concentration of digoxin increased
*	Enalapril	Enhanced hypotensive effect; increased risk of severe hyperkalaemia (monitor plasma potassium concentration with low-dose spironolactone in heart failure)
	Fluphenazine	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of diuretic effect
	Ibuprofen	Risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
*	Lithium	Reduced lithium excretion (increased plasma lithium concentration and risk of toxicity)
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Nitrous oxide	Enhanced hypotensive effect
*	Potassium salts	Risk of hyperkalaemia
	Prednisolone	Antagonism of diuretic effect
	Propranolol	Enhanced hypotensive effect
	Sodium nitroprusside	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
	Timolol	Enhanced hypotensive effect
	Verapamil	Enhanced hypotensive effect

Stavudine		
*	Didanosine	Increased risk of adverse effects
	Doxorubicin	Doxorubicin may inhibit effects of stavudine
*	Ribavirin	Possibly inhibited effects of stavudine
*	Zidovudine	May inhibit effect of stavudine (avoid concomitant use)
Streptomycin		
*	Alcuronium	Enhanced muscle relaxant effect
	Amphotericin B	Increased risk of nephrotoxicity
	Capreomycin	Increased risk of nephrotoxicity and ototoxicity
*	Ciclosporin	Increased risk of nephrotoxicity
*	Cisplatin	Increased risk of nephrotoxicity and possibly of ototoxicity
*	Furosemide	Increased risk of ototoxicity
*	Neostigmine	Antagonism of effect of neostigmine
*	Pyridostigmine	Antagonism of effect of pyridostigmine
*	Suxamethonium	Enhanced muscle relaxant effect
	Vancomycin	Increased risk of nephrotoxicity and ototoxicity
*	Vecuronium	Enhanced muscle relaxant effect
Sulfadiazine		
*	Ciclosporin	Plasma ciclosporin concentration possibly reduced; increased risk of nephrotoxicity
	Glibenclamide	Effect of glibenclamide rarely enhanced
	Methotrexate	Risk of methotrexate toxicity increased
	Phenytoin	Plasma phenytoin concentration possibly increased
*	Pyrimethamine	Increased antifolate effect
*	Sulfadoxine + pyrimethamine	Increased antifolate effect
	Thiopental	Enhanced effects of thiopental
*	Warfarin	Enhanced anticoagulant effect
Sulfadoxine + pyrimethamine		
*	Artemether + lumefantrine	Manufacturer of artemether + lumefantrine advises avoid concomitant use
*	Ciclosporin	Increased risk of nephrotoxicity
	Glibenclamide	Effect of glibenclamide rarely enhanced
*	Methotrexate	Antifolate effect of methotrexate increased; risk of methotrexate toxicity increased
*	Phenytoin	Plasma phenytoin concentration possibly increased; increased antifolate effect
*	Sulfadiazine	Increased antifolate effect
*	Sulfamethoxazole + trimethoprim	Increased antifolate effect
	Thiopental	Enhanced effects of thiopental
*	Trimethoprim	Increased antifolate effect
*	Warfarin	Enhanced anticoagulant effect
Sulfamethoxazole + trimethoprim		
*	Azathioprine	Increased risk of haematological toxicity
*	Ciclosporin	Increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim
	Dapsone	Plasma concentration of both dapsone and trimethoprim may increase with concomitant use
	Digoxin	Plasma concentration of digoxin possibly increased
	Glibenclamide	Effect of glibenclamide rarely enhanced

	Lamivudine	Plasma concentration of lamivudine increased (avoid concomitant use of high-dose sulfamethoxazole + trimethoprim)
*	Mercaptopurine	Increased risk of haematological toxicity
*	Methotrexate	Antifolate effect of methotrexate increased (avoid concomitant use); risk of methotrexate toxicity increased
*	Phenytoin	Antifolate effect and plasma phenytoin concentration increased
	Procainamide	Increased plasma procainamide concentration
*	Pyrimethamine	Increased antifolate effect
*	Sulfadoxine + pyrimethamine	Increased antifolate effect
	Thiopental	Enhanced effects of thiopental
*	Warfarin	Enhanced anticoagulant effect
Sulfasalazine		
	Azathioprine	Possibly increased risk of leukopenia
	Digoxin	Absorption of digoxin possibly reduced
	Folic acid and Folinic acid	Possibly reduced absorption of folic acid
	Mercaptopurine	Possibly increased risk of leukopenia
Suxamethonium		
*	Amikacin	Enhanced effects of suxamethonium
*	Clindamycin	Enhanced effects of suxamethonium
	Cyclophosphamide	Enhanced effects of suxamethonium
	Digoxin	Risk of ventricular arrhythmias
*	Gentamicin	Enhanced muscle relaxant effect
	Halothane	Enhanced effects of suxamethonium
	Lidocaine	Neuromuscular blockade enhanced and prolonged (interaction less likely when lidocaine used topically)
	Lithium	Enhanced muscle relaxant effect
	Magnesium (parenteral)	Enhanced muscle relaxant effect
	Metoclopramide	Enhanced effects of suxamethonium
	Neostigmine	Effect of suxamethonium enhanced
*	Paromomycin	Possibly enhanced effects of suxamethonium
*	Procainamide	Enhanced muscle relaxant effect
	Propranolol	Enhanced muscle relaxant effect
	Pyridostigmine	Effect of suxamethonium enhanced
*	Quinidine	Enhanced muscle relaxant effect
	Quinine	Possibly enhanced effects of suxamethonium
*	Streptomycin	Enhanced muscle relaxant effect
*	Vancomycin	Enhanced effects of suxamethonium
	Verapamil	Enhanced effects of suxamethonium
Tamoxifen		
*	Warfarin	Enhanced anticoagulant effect
Tenofovir		
	Didanosine	Plasma concentration of didanosine increased (increased risk of toxicity — avoid concomitant use)
*	Lopinavir	Plasma concentration of tenofovir increased
Testosterone		
	Glibenclamide	Hypoglycaemic effect possibly enhanced
	Insulins	Hypoglycaemic effect possibly enhanced
	Metformin	Hypoglycaemic effect possibly enhanced
*	Warfarin	Enhanced anticoagulant effect

Thiopental

	Acetazolamide	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amitriptyline	Increased risk of arrhythmias and hypotension
	Amlodipine	Enhanced hypotensive effect
	Atenolol	Enhanced hypotensive effect
*	Chlorpromazine	Enhanced hypotensive effect
	Clomipramine	Increased risk of arrhythmias and hypotension
	Diazepam	Enhanced sedative effect
	Enalapril	Enhanced hypotensive effect
*	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
*	Haloperidol	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Isoniazid	Possible potentiation of isoniazid hepatotoxicity
	Isosorbide dinitrate	Enhanced hypotensive effect
	Methyldopa	Enhanced hypotensive effect
	Nifedipine	Enhanced hypotensive effect
	Propranolol	Enhanced hypotensive effect
	Silver sulfadiazine	Enhanced effects of thiopental
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Sulfadiazine	Enhanced effects of thiopental
	Sulfadoxine + pyrimethamine	Enhanced effects of thiopental
	Sulfamethoxazole + trimethoprim	Enhanced effects of thiopental
	Timolol	Enhanced hypotensive effect
	Vancomycin	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
*	Verapamil	Enhanced hypotensive effect and AV delay

Timolol

NOTE. Systemic absorption may follow topical application of timolol to the eye.

	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect
	Amiloride	Enhanced hypotensive effect
	Amlodipine	Enhanced hypotensive effect
	Chlorpromazine	Enhanced hypotensive effect
	Diazepam	Enhanced hypotensive effect
	Digoxin	Increased AV block and bradycardia
	Enalapril	Enhanced hypotensive effect
*	Epinephrine	Severe hypertension
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glibenclamide	Timolol may mask warning signs of hypoglycaemia such as tremor
	Glyceryl trinitrate	Enhanced hypotensive effect
	Halothane	Enhanced hypotensive effect
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect

	Insulins	Enhanced hypoglycaemic effect; timolol may mask warning signs of hypoglycaemia such as tremor
	Isosorbide dinitrate	Enhanced hypotensive effect
	Ketamine	Enhanced hypotensive effect
	Levodopa	Enhanced hypotensive effect
*	Lidocaine	Increased myocardial depression (interaction less likely when lidocaine used topically)
	Mefloquine	Increased risk of bradycardia
	Metformin	Timolol may mask warning signs of hypoglycaemia such as tremor
	Methyldopa	Enhanced hypotensive effect
*	Nifedipine	Enhanced hypotensive effect; possibly severe hypotension and heart failure
	Nitrous oxide	Enhanced hypotensive effect
	Pilocarpine	Increased risk of arrhythmias
*	Procainamide	Increased myocardial depression
*	Quinidine	Increased myocardial depression
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Thiopental	Enhanced hypotensive effect
*	Verapamil	Asystole, severe hypotension, and heart failure
Trimethoprim		
*	Azathioprine	Increased risk of haematological toxicity
*	Ciclosporin	Increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim
	Dapsone	Plasma concentration of both dapsone and trimethoprim may increase with concomitant use
	Digoxin	Plasma concentration of digoxin possibly increased
	Glibenclamide	Effects of glibenclamide rarely enhanced
*	Mercaptopurine	Increased risk of haematological toxicity
*	Methotrexate	Antifolate effect of methotrexate increased (avoid concomitant use)
*	Phenytoin	Antifolate effect and plasma phenytoin concentration increased
	Procainamide	Increased plasma procainamide concentration
*	Pyrimethamine	Increased antifolate effect
*	Sulfadoxine + pyrimethamine	Increased antifolate effect
	Warfarin	Possibly enhanced anticoagulant effect
Vaccine, Influenza		
	Dexamethasone	High doses of dexamethasone impair immune response
	Hydrocortisone	High doses of hydrocortisone impair immune response
	Phenytoin	Enhanced effect of phenytoin
	Prednisolone	High doses of prednisolone impair immune response
	Warfarin	Effect of warfarin occasionally enhanced
Vaccine, Live		
	NOTE. Vaccine, Live includes BCG, Cholera (oral), Measles, MMR, Poliomyelitis (oral), Rubella, Typhoid, Varicella, and Yellow fever vaccines.	
	Asparaginase	Avoid use of live vaccines with asparaginase (impairment of immune response)

*	Azathioprine	Avoid use of live vaccines with azathioprine (impairment of immune response)
	Bleomycin	Avoid use of live vaccines with bleomycin (impairment of immune response)
	Chlorambucil	Avoid use of live vaccines with chlorambucil (impairment of immune response)
*	Ciclosporin	Avoid use of live vaccines with ciclosporin (impairment of immune response)
	Cisplatin	Avoid use of live vaccines with cisplatin (impairment of immune response)
	Cyclophosphamide	Avoid use of live vaccines with cyclophosphamide (impairment of immune response)
	Cytarabine	Avoid use of live vaccines with cytarabine (impairment of immune response)
	Dacarbazine	Avoid use of live vaccines with dacarbazine (impairment of immune response)
	Dactinomycin	Avoid use of live vaccines with dactinomycin (impairment of immune response)
	Daunorubicin	Avoid use of live vaccines with daunorubicin (impairment of immune response)
*	Dexamethasone	High doses of dexamethasone impair immune response; avoid use of live vaccines with dexamethasone
	Doxorubicin	Avoid use of live vaccines with doxorubicin (impairment of immune response)
	Etoposide	Avoid use of live vaccines with etoposide (impairment of immune response)
	Fluorouracil	Avoid use of live vaccines with fluorouracil (impairment of immune response)
*	Hydrocortisone	High doses of hydrocortisone impair immune response; avoid use of live vaccines with hydrocortisone
*	Immunoglobulin (human), Anti-D	Avoid use of live virus vaccine during *4 weeks before* or during *3 months after* 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
	Immunoglobulin, Human normal	Avoid use of live vaccine during *3 weeks before* or during *3 months after* injection of human normal immunoglobulin (impairment of immune response)
	Mercaptopurine	Avoid use of live vaccines with mercaptopurine (impairment of immune response)
	Methotrexate	Avoid use of live vaccines with methotrexate (impairment of immune response)
*	Prednisolone	High doses of prednisolone impair immune response; avoid use of live vaccines with prednisolone
	Procarbazine	Avoid use of live vaccines with procarbazine (impairment of immune response)
	Vinblastine	Avoid use of live vaccines with vinblastine (impairment of immune response)
	Vincristine	Avoid use of live vaccines with vincristine (impairment of immune response)
Valproic acid		
	Acetylsalicylic acid	Enhancement of effect of valproic acid
*	Amitriptyline	Antagonism of anticonvulsant effect (convulsive threshold lowered)

	Carbamazepine	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid reduced; plasma concentration of active metabolite of carbamazepine increased
*	Chloroquine	Possibly increased risk of convulsions
*	Chlorpromazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Clomipramine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
	Erythromycin	Metabolism of valproic acid possibly inhibited (increased plasma concentration)
	Ethosuximide	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of ethosuximide possibly increased
*	Fluphenazine	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Haloperidol	Antagonism of anticonvulsant effect (convulsive threshold lowered)
*	Mefloquine	Antagonism of anticonvulsant effect
	Phenobarbital	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid reduced; phenobarbital concentration increased
	Phenytoin	May be enhanced toxicity without corresponding increase in antiepileptic effect; plasma concentration of valproic acid reduced; plasma concentration of phenytoin increased or possibly reduced
	Warfarin	Anticoagulant effect possibly enhanced
	Zidovudine	Plasma concentration of zidovudine possibly increased (risk of toxicity)
Vancomycin		
	Amikacin	Increased risk of nephrotoxicity and ototoxicity
	Amphotericin B	Possibly increased risk of nephrotoxicity
	Capreomycin	Increased risk of nephrotoxicity and ototoxicity
*	Ciclosporin	Increased risk of nephrotoxicity
	Cisplatin	Increased risk of nephrotoxicity and possibly of ototoxicity
	Furosemide	Increased risk of ototoxicity
	Gentamicin	Increased risk of nephrotoxicity and ototoxicity
	Halothane	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
	Ketamine	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
	Nitrous oxide	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
	Paromomycin	Increased risk of ototoxicity
	Streptomycin	Increased risk of nephrotoxicity and ototoxicity
*	Suxamethonium	Enhanced effects of suxamethonium
	Thiopental	Hypersensitivity-like reactions can occur with concomitant intravenous vancomycin
Vecuronium		
*	Amikacin	Enhanced effects of vecuronium
	Carbamazepine	Antagonism of muscle relaxant effect (recovery from neuromuscular blockade accelerated)
*	Clindamycin	Enhanced muscle relaxant effect

*	Gentamicin	Enhanced muscle relaxant effect
	Halothane	Enhanced effects of vecuronium
	Lithium	Enhanced muscle relaxant effect
	Magnesium (parenteral)	Enhanced muscle relaxant effect
	Neostigmine	Antagonism of muscle relaxant effect
	Nifedipine	Enhanced muscle relaxant effect
	Phenytoin	Antagonism of muscle relaxant effect (accelerated recovery from neuromuscular blockade)
*	Procainamide	Enhanced muscle relaxant effect
	Propranolol	Enhanced muscle relaxant effect
	Pyridostigmine	Antagonism of muscle relaxant effect
*	Quinidine	Enhanced muscle relaxant effect
*	Streptomycin	Enhanced muscle relaxant effect
	Verapamil	Enhanced muscle relaxant effect
Verapamil		
	Acetazolamide	Enhanced hypotensive effect
	Alcohol	Enhanced hypotensive effect; plasma concentration of alcohol possibly increased by verapamil
	Alcuronium	Enhanced muscle relaxant effect
	Amiloride	Enhanced hypotensive effect
	Amitriptyline	Possibly increased plasma concentration of amitriptyline
*	Atenolol	Asystole, severe hypotension, and heart failure
*	Carbamazepine	Enhanced effect of carbamazepine
	Chlorpromazine	Enhanced hypotensive effect
*	Ciclosporin	Increased plasma ciclosporin concentration
	Clomipramine	Possibly increased plasma concentration of clomipramine
	Contraceptives, Oral	Antagonism of hypotensive effect by estrogens
	Dexamethasone	Antagonism of hypotensive effect
	Diazepam	Enhanced hypotensive effect
*	Digoxin	Increased plasma concentration of digoxin; increased AV block and bradycardia
	Enalapril	Enhanced hypotensive effect
*	Erythromycin	Possible inhibition of metabolism of verapamil (increased risk of toxicity)
	Fluphenazine	Enhanced hypotensive effect
	Furosemide	Enhanced hypotensive effect
	Glyceryl trinitrate	Enhanced hypotensive effect
	Grapefruit juice	Increased plasma verapamil concentration
	Haloperidol	Enhanced hypotensive effect
*	Halothane	Enhanced hypotensive effect and AV delay
	Hydralazine	Enhanced hypotensive effect
	Hydrochlorothiazide	Enhanced hypotensive effect
	Hydrocortisone	Antagonism of hypotensive effect
	Ibuprofen	Antagonism of hypotensive effect
	Isosorbide dinitrate	Enhanced hypotensive effect
*	Ketamine	Enhanced hypotensive effect and AV delay
	Levodopa	Enhanced hypotensive effect
*	Lidocaine	Increased risk of myocardial depression (interaction less likely when lidocaine used topically)
	Lithium	Neurotoxicity may occur without increased plasma lithium concentration
	Mefloquine	Possibly increased risk of bradycardia
	Methyldopa	Enhanced hypotensive effect
*	Nitrous oxide	Enhanced hypotensive effect and AV delay

*	Phenobarbital	Effect of verapamil probably reduced
	Phenytoin	Reduced effect of verapamil
	Prednisolone	Antagonism of hypotensive effect
*	Propranolol	Asystole, severe hypotension and heart failure
*	Quinidine	Increased plasma quinidine concentration (extreme hypotension may occur)
*	Rifampicin	Accelerated metabolism of verapamil (plasma concentration significantly reduced)
*	Ritonavir	Plasma concentration possibly increased by ritonavir
*	Simvastatin	Increased risk of myopathy
	Sodium nitroprusside	Enhanced hypotensive effect
	Spironolactone	Enhanced hypotensive effect
	Suxamethonium	Enhanced effects of suxamethonium
*	Thiopental	Enhanced hypotensive effect and AV delay
*	Timolol	Asystole, severe hypotension, and heart failure
	Vecuronium	Enhanced muscle relaxant effect
Vinblastine		
*	Bleomycin	Increased risk of cardiovascular toxicity
*	Erythromycin	Increased toxicity of vinblastine (avoid concomitant use)
	Phenytoin	Possibly reduced absorption of phenytoin
	Vaccine, Live	Avoid use of live vaccines with vinblastine (impairment of immune response)
Vincristine		
	Nifedipine	Possibly reduced metabolism of vincristine
	Phenytoin	Possibly reduced absorption of phenytoin
	Vaccine, Live	Avoid use of live vaccines with vincristine (impairment of immune response)
Vitamin D		
	see Ergocalciferol	
Warfarin		
	NOTE. Major changes in the diet (especially involving salads and vegetables) and in alcohol consumption may affect anticoagulant control.	
*	Acetylsalicylic acid	Increased risk of bleeding due to antiplatelet effect
*	Alcohol	Enhanced anticoagulant effect with large amounts of alcohol; major changes in alcohol consumption may affect anticoagulant control
	Allopurinol	Anticoagulant effect possibly enhanced
*	Amitriptyline	Enhanced or reduced anticoagulant effect
	Amoxicillin	Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of amoxicillin
	Ampicillin	Studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of ampicillin
*	Azathioprine	Anticoagulant effect possibly reduced
*	Azithromycin	Possibly enhanced anticoagulant effect of warfarin
*	Carbamazepine	Accelerated metabolism of warfarin (reduced anticoagulant effect)
*	Cefazolin	Possibly enhanced anticoagulant effect
*	Cefixime	Possibly enhanced anticoagulant effect
*	Ceftazidime	Possibly enhanced anticoagulant effect
*	Ceftriaxone	Possibly enhanced anticoagulant effect

*	Chloramphenicol	Enhanced anticoagulant effect
*	Ciprofloxacin	Enhanced anticoagulant effect
*	Clomipramine	Enhanced or reduced anticoagulant effect
*	Contraceptives, Oral	Antagonism of anticoagulant effect by estrogens and progestogens
*	Dexamethasone	Anticoagulant effect possibly enhanced or reduced (high-dose dexamethasone enhances anticoagulant effect)
*	Doxycycline	Anticoagulant effect possibly enhanced
*	Erythromycin	Enhanced anticoagulant effect
*	Etoposide	Possibly enhanced anticoagulant effect
*	Fluconazole	Enhanced anticoagulant effect
*	Fluorouracil	Anticoagulant effect possibly enhanced
*	Fluoxetine	Anticoagulant effect possibly enhanced
*	Glibenclamide	Possibly enhanced hypoglycaemic effect and changes to anticoagulant effect
*	Griseofulvin	Reduced anticoagulant effect
*	Hydrocortisone	Anticoagulant effect possibly enhanced or reduced (high-dose hydrocortisone enhances anticoagulant effect)
*	Ibuprofen	Anticoagulant effect possibly enhanced
*	Levamisole	Anticoagulant effect possibly enhanced
	Levofloxacin	Possibly enhanced anticoagulant effect
*	Levonorgestrel	Antagonism of anticoagulant effect
*	Levothyroxine	Enhanced anticoagulant effect
*	Medroxyprogesterone	Antagonism of anticoagulant effect
*	Mercaptopurine	Anticoagulant effect possibly reduced
*	Metronidazole	Enhanced anticoagulant effect
*	Miconazole	Enhanced anticoagulant effect
*	Nevirapine	Enhanced or reduced anticoagulant effect
*	Norethisterone	Antagonism of anticoagulant effect
*	Ofloxacin	Enhanced anticoagulant effect
	Paracetamol	Prolonged regular use of paracetamol possibly enhances anticoagulant effect
*	Phenobarbital	Metabolism of warfarin accelerated (reduced anticoagulant effect)
*	Phenytoin	Accelerated metabolism of warfarin (possibility of reduced anticoagulant effect, but enhancement also reported)
*	Phytomenadione	Antagonism of anticoagulant effect
*	Prednisolone	Anticoagulant effect enhanced or reduced (high-dose prednisolone enhances anticoagulant effect)
	Proguanil	Isolated reports of enhanced anticoagulant effect
*	Quinidine	Anticoagulant effect may be enhanced
*	Rifampicin	Accelerated metabolism of warfarin (reduced anticoagulant effect)
*	Ritonavir	Plasma concentration possibly increased by ritonavir
	Saquinavir	Possibly enhanced anticoagulant effect
*	Silver sulfadiazine	Enhanced anticoagulant effect
*	Simvastatin	Enhanced anticoagulant effect
*	Sulfadiazine	Enhanced anticoagulant effect
*	Sulfadoxine + pyrimethamine	Enhanced anticoagulant effect
*	Sulfamethoxazole + trimethoprim	Enhanced anticoagulant effect
*	Tamoxifen	Enhanced anticoagulant effect
*	Testosterone	Enhanced anticoagulant effect

	Trimethoprim	Possibly enhanced anticoagulant effect
	Vaccine, Influenza	Effect of warfarin occasionally enhanced
	Valproic acid	Anticoagulant effect possibly enhanced

Yellow fever vaccine

see Vaccine, live

Zidovudine

NOTE. Increased risk of toxicity with nephrotoxic and myelosuppressive drugs.

*	Fluconazole	Increased plasma concentration of zidovudine (increased risk of toxicity)
	Ibuprofen	Increased risk of haematological toxicity
	Methadone	Possibly increased plasma concentration of zidovudine
	Phenytoin	Plasma phenytoin concentration increased or decreased by zidovudine
	Pyrimethamine	Increased antifolate effect
*	Ribavirin	Possibly inhibited effect of zidovudine
	Rifampicin	Manufacturer of zidovudine advises avoid concomitant use
*	Stavudine	May inhibit effect of stavudine (avoid concomitant use)
	Valproic acid	Plasma concentration of zidovudine possibly increased (risk of toxicity)

Zinc sulfate

Calcium salts	Reduced absorption of zinc sulfate
Ciprofloxacin	Reduced absorption of ciprofloxacin
Ferrous salts	Absorption of zinc and of oral ferrous salts reduced
Levofloxacin	Reduced absorption of levofloxacin
Ofloxacin	Reduced absorption of ofloxacin
Penicillamine	Absorption of both drugs reduced

Appendix 2: 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, suboptimal treatment, and treatment failures may all impose 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 trimester* 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 labour may have adverse effects on labour or on the neonate after delivery. Few drugs have been shown conclusively to be teratogenic in man but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available where there is a known risk of certain defects.

Prescribing in pregnancy

If possible, counselling 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 which 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 multi-component drugs.

The following table lists drugs which 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 does not imply safety

Medicine	Comment
Abacavir	Toxicity in animal studies; *see* section 6.4.2
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 labour 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; *see* section 6.1.1 First trimester: avoid in nematode infections; *see* section 6.1.1
Alcohol	First, and second trimesters: Regular daily drinking is teratogenic (fetal alcohol syndrome) and may cause growth retardation; occasional single drinks are probably safe Third trimester: Withdrawal may occur in babies of alcoholic mothers
Alcuronium	Does not cross placenta in significant amounts; use only if potential benefit outweighs risk
Allopurinol	Toxicity not reported; use only if no safer alternative and disease carries risk for mother or child
Amiloride	Not used to treat hypertension in pregnancy

Medicine	Comment
Amitriptyline	Manufacturer advises 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
Amodiaquine	Use only if no safer alternative
Amoxicillin	Not known to be harmful
Amoxicillin + clavulanic acid	See Amoxicillin
Amphotericin B	Not known to be harmful but use only if potential benefit outweighs risk
Ampicillin	Not known to be harmful
Artemether	First trimester: Avoid
Artemether + lumefantrine	See Artemether
Artesunate	First trimester: Avoid
Asparaginase	Avoid; *see* section 8.2
Atenolol	May cause intrauterine growth restriction, neonatal hypoglycaemia, and bradycardia; risk greater in severe hypertension; *see* section 12.3
Atropine	Not known to be harmful
Azathioprine	Transplant patients should not discontinue azathioprine on becoming pregnant; use in pregnancy should be carefully supervised; there is no evidence that azathioprine is teratogenic but premature birth and low birth weight and spontaneous abortion reported following maternal or paternal exposure
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

Medicine	Comment
Benznidazole	First trimester: avoid
Benzylpenicillin	Not known to be harmful
Betamethasone	Benefit of treatment, for example in asthma, outweighs risk
Bleomycin	Avoid (teratogenic and carcinogenic in animal studies); *see* section 8.2
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
Calcium folinate	Manufacturer advises use only if potential benefit outweighs risk
Carbamazepine	First trimester: Risk of teratogenesis including increased risk of neural tube defects (counselling and screening and adequate folate supplements advised, for example, 5 mg daily); risk of teratogenicity greater if more than one antiepileptic used; *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
Cefazolin	Not known to be harmful
Cefixime	Not known to be harmful
Ceftazidime	Not known to be harmful
Ceftriaxone	Not known to be harmful
Chlorambucil	Avoid; use effective contraception during administration to men or women; *see* section 8.2
Chloramphenicol	Third trimester: Neonatal "grey" 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 in neonate occasionally reported

Medicine	Comment
Ciclosporin	There is less experience of ciclosporin in pregnancy but it does not appear to be any more harmful than azathioprine; use in pregnancy should be supervised in specialist units
Ciprofloxacin	Avoid (arthropathy in animal studies); safer alternatives available
Cisplatin	Avoid (teratogenic and toxic in animal studies); *see* section 8.2
Clindamycin	Not known to be harmful
Clomifene	Possible effects on fetal development
Clomipramine	Manufacturer advises avoid unless essential, particularly during first and third trimesters
Cloxacillin	Not known to be harmful
Codeine	Third trimester: Depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour
Contraceptives, Oral	Epidemiological evidence suggests no harmful effects on fetus
Cyclophosphamide	Avoid; use effective contraception during and for at least 3 months after administration to men or women; *see* section 8.2
Cytarabine	Avoid (teratogenic in animal studies); *see* section 8.2
Dacarbazine	Avoid (carcinogenic and teratogenic in animal studies); use effective contraception during and for at least 6 months after administration to men or women; *see* section 8.2
Dactinomycin	Avoid (teratogenic in animal studies); *see* section 8.2
Dapsone	Third trimester: Neonatal haemolysis and methaemoglobinaemia; folic acid, 5 mg daily, should be given to mother
Daunorubicin	Avoid (teratogenic and carcinogenic in animal studies); *see* section 8.2
Deferoxamine	Teratogenic in animal studies; manufacturer advises use only if potential benefit outweighs risk

Medicine	Comment
Dexamethasone	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 labour; monitor closely if fluid retention
Diazepam	Avoid regular use (risk of neonatal withdrawal symptoms); use only if clear indication such as seizure control (high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression)
Didanosine	Avoid if possible in first trimester; increased risk of lactic acidosis and hepatic steatosis; *see* section 6.4.2.1
Diethylcarbamazine	Avoid: Delay treatment until after delivery
Digoxin	May need dosage adjustment
Diloxanide	Defer treatment until after first trimester
Doxorubicin	Avoid (teratogenic and toxic in animal studies); with liposomal product use effective contraception during and for at least 6 months after administration to men or women; *see* section 8.2
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); *see* section 6.4.2.2
Eflornithine	Avoid
Emtricitabine	No information available; use only if essential; *see* section 6.4.2.1
Enalapril	Avoid; may adversely affect fetal and neonatal blood pressure control and renal function; also possible skull defects and oligohydramnios; toxicity in animal studies
Ephedrine	Increased fetal heart rate reported with parenteral ephedrine
Ergocalciferol	High doses teratogenic in animals but therapeutic doses unlikely to be harmful

Medicine	Comment
Erythromycin	Not known to be harmful
Estradiol cypionate	Epidemiological evidence suggests no harmful effects on fetus; *see* Contraceptives, Oral
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 antiepileptic used; *see* section 5
Etoposide	Avoid (teratogenic in animal studies); *see* section 8.2
Fluconazole	Avoid (multiple congenital abnormalities reported with long-term high doses)
Flucytosine	Teratogenic in animal studies; manufacturer advises use only if potential benefit outweighs risk
Fluorouracil	Avoid (teratogenic); *see* section 8.2
Fluoxetine	Manufacturer advises use only if potential benefit outweighs risk; risk of neonatal withdrawal
Fluphenazine	Third trimester: Extrapyramidal effects in neonate occasionally reported
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 hypoglycaemia; 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; *see* Appendix 1); also men should avoid fathering a child during and for at least 6 months after administration

Medicine	Comment
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 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 labour; monitor closely if fluid retention
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 labour
Imipenem + cilastatin	Use only if potential benefit outweighs risk (toxicity in animal studies)
Indinavir	Avoid if possible in first trimester; theoretical risk of hyperbilirubinaemia and renal stones in neonates if used at term; *see* section 6.4.2.3
Insulins	Insulin requirements should be assessed frequently by an experienced diabetes clinician
Iodine	Second and third trimesters: Neonatal goitre and hypothyroidism
Ipratropium bromide	Not known to be harmful
Isoniazid	Not known to be harmful
Ivermectin	Delay treatment until after delivery; *see* section 6.1.2
Ketamine	Third trimester: Depresses neonatal respiration

Medicine	Comment
Lamivudine	Avoid if possible in first trimester; benefit of treatment considered to outweigh risk in second and third trimesters; *see* section 6.4.2.1
Levamisole	Third trimester: Avoid
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
Lithium	First trimester: Avoid if possible (risk of teratogenicity including cardiac abnormalities) Second and third trimesters: Dose requirements increased (but on delivery return to normal abruptly); close monitoring of serum lithium concentration advised (risk of toxicity in neonate)
Lopinavir + ritonavir	Avoid if possible in first trimester; avoid oral solution due to high propylene glycol content; *see* section 6.4.2.3
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; *see* section 6.1.1 First trimester: Avoid in nematode infections; *see* section 6.1.1
Medroxyprogesterone acetate	Avoid (genital malformations and cardiac defects reported in male and female fetuses); inadvertent use of depot medroxyprogesterone acetate contraceptive injection in pregnancy unlikely to harm fetus
Mefloquine	Use only if other antimalarials inappropriate, *see* section 6.5.3

Medicine	Comment
Melarsoprol	Avoid
Mercaptopurine	Avoid (teratogenic); *see* section 8.2
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 labour
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
Metronidazole	Avoid high-dose regimens
Mifepristone	If treatment fails, pregnancy must be terminated by another method
Misoprostol	Potent uterine stimulant; may be teratogenic; if medical abortion fails, pregnancy must be terminated by another method
Morphine	Third trimester: Depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour
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; *see* section 6.4.2.3
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; *see* section 6.4.2.2
Niclosamide	*T. solium* infections in pregnancy should be treated immediately; *see* section 6.1.1

Medicine	Comment
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 labour)
Nifurtimox	First trimester: Avoid
Nitrofurantoin	Third trimester: May produce neonatal haemolysis if used at term
Nitrous oxide	Third trimester: Depresses neonatal respiration
Norethisterone	In oral contraceptives, epidemiological evidence suggests no harmful effects on fetus; in higher doses masculinization of female fetuses and other defects reported
Nystatin	No information available, but absorption from gastrointestinal tract negligible
Ofloxacin	Avoid (arthropathy in animal studies); safer alternatives available
Oxamniquine	If immediate treatment not required, schistosomiasis treatment should be delayed until after delivery; *see* section 6.1.3
Paracetamol	Not known to be harmful
Paromomycin	Second and third trimesters: Auditory or vestibular nerve damage possible; no information on use in humans
Penicillamine	Fetal abnormalities reported rarely; avoid if possible
Pentamidine isetionate	Potentially fatal visceral leishmaniasis must be treated without delay; should not be withheld in trypanosomiasis even if evidence of meningo-encephalitic involvement; potentially fatal *P. carinii* (*P. jiroveci*) pneumonia must be treated without delay
Pentavalent antimony compounds	Potentially fatal visceral leishmaniasis must be treated without delay

Medicine	Comment
Phenobarbital	First and third trimesters: Congenital malformations — risk of teratogenicity greater if more than one antiepileptic 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; *see* section 5
Phenoxymethylpenicillin	Not known to be harmful
Phenytoin	First and third trimesters: Congenital malformations (screening advised); adequate folate supplements should be given to mother (for example, folic acid 5 mg daily); risk of teratogenicity greater if more than one antiepileptic 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 NOTE. Caution in interpreting plasma phenytoin concentrations — bound phenytoin may be reduced but free (or effective) phenytoin unchanged; *see* section 5
Phytomenadione	No specific information available; use only if potential benefit outweighs risk
Podophyllum resin	Avoid; neonatal death and teratogenesis have been reported
Polyvidone iodine	Second and third trimesters: Sufficient iodine may be absorbed to affect the fetal thyroid
Potassium iodide	Second and third trimesters: Neonatal goitre and hypothyroidism
Praziquantel	*T. solium* infections in pregnancy should be treated immediately; *see* section 6.1.1; benefit of treatment in schistosomiasis outweighs risk; *see* section 6.1.3; if immediate treatment not considered essential for fluke infections, treatment should be delayed until after delivery; *see* section 6.1.3
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 labour; monitor closely if fluid retention

Medicine	Comment
Primaquine	Third trimester: Neonatal haemolysis and methaemoglobinaemia; delay treatment until after delivery
Procarbazine	Avoid (teratogenic in animal studies and isolated reports in humans); *see* section 8.2
Proguanil	Benefit of prophylaxis and of treatment outweighs risk; adequate folate supplements should be given to mother
Promethazine	No evidence of teratogenicity
Propranolol	May cause intrauterine growth restriction, neonatal hypoglycaemia, and bradycardia; risk greater in severe hypertension; *see* section 12.3
Propylthiouracil	Second and third trimesters: Neonatal goitre and hypothyroidism
Pyrazinamide	Use only if potential benefit outweighs risk
Pyridostigmine	Third trimester: Neonatal myasthenia with large doses
Pyrimethamine	First trimester: Theoretical teratogenic risk (folate antagonist); adequate folate supplements should be given to the mother; avoid in pneumocystosis and toxoplasmosis; *see* Sulfadiazine
Quinidine	Not known to be harmful at therapeutic doses
Quinine	First trimester: High doses are teratogenic; but in malaria benefit of treatment outweighs risk
Ranitidine	Not known to be harmful
Retinol	First trimester: Excessive doses may be teratogenic; *see* section 27
Ribavirin	Avoid (teratogenic); use effective contraception during and for at least 7 months after administration to men or women; *see* section 6.4.3
Rifampicin	First trimester: Very high doses teratogenic in animal studies Third trimester: Risk of neonatal bleeding may be increased
Ritonavir	*See* Lopinavir + ritonavir

Medicine	Comment
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; *see* section 6.4.2.3
Silver sulfadiazine	Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded
Simvastatin	Avoid — congenital anomalies reported; decreased synthesis of cholesterol possibly affects fetal development
Sodium nitroprusside	Potential for accumulation of cyanide in fetus — avoid prolonged use
Sodium valproate	*see* Valproic acid
Spironolactone	Toxicity in animal studies
Stavudine	Avoid if possible in first trimester; increased risk of lactic acidosis and hepatic steatosis; *see* section 6.4.2.1
Streptokinase	Possibility of premature separation of placenta in first 18 weeks; theoretical possibility of fetal haemorrhage throughout pregnancy; risk of maternal haemorrhage on postpartum use
Streptomycin	Second and third trimesters: Auditory or vestibular nerve damage; avoid unless essential (if given, serum streptomycin concentration monitoring essential)
Sulfadiazine	Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded In toxoplasmosis, avoid in first trimester, but may be given in second and third trimester if danger of congenital transmission
Sulfadoxine + pyrimethamine	In malaria, benefit of prophylaxis and treatment outweigh risk First trimester: possible teratogenic risk (pyrimethamine is a folate antagonist)

Medicine	Comment
	Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded; *see* section 6.5.3.1
Sulfamethoxazole + trimethoprim	First trimester: Teratogenic risk (trimethoprim is a folate antagonist) Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded
Sulfasalazine	Third trimester: Theoretical risk of neonatal haemolysis; adequate folate supplements should be given to mother
Suramin sodium	In onchocerciasis, delay treatment until after delivery; in *T. brucei rhodesiense,* treatment should be given even if evidence of meningoencephalopathic involvement
Suxamethonium	Mildly prolonged maternal paralysis may occur
Tamoxifen	Avoid (possible effects on fetal development); use effective contraception during treatment and for at least 2 months after administration to women
Tenofovir	No information available; use only if potential benefit outweighs risk; *see* section 6.4.2.1
Testosterone	Masculinization of female fetus
Tetracycline	First trimester: Effects on skeletal development in animal studies Second and third trimesters: Dental discoloration; maternal hepatotoxicity with large doses
Thiopental	Third trimester: Depresses neonatal respiration; dose should not exceed 250 mg
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; *see* section 19.3
Vaccine, Influenza	Not known to be harmful

Medicine	Comment
Vaccine, Measles	First trimester: Theoretical risk of congenital malformations, but need for vaccination may outweigh possible risk to fetus; *see* section 19.3; 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; *see* section 19.3
Vaccine, Rubella	Avoid; pregnancy should be avoided for 1 month after immunization
Vaccine, Varicella	Avoid; pregnancy should be avoided for 3 months after immunization
Vaccine, Yellow fever	First trimester: Theoretical risk of congenital malformations, however need for vaccination may outweigh possible risk to fetus especially after the 6th month of pregnancy; pregnant women should be advised *not* to travel to areas where there is a risk of exposure to yellow fever; *see* section 19.3
Valproic acid	First and third trimesters: Increased risk of congenital malformations and developmental delay (counselling and screening advised — folic acid supplements may reduce risk of neural tube defects); risk of teratogenicity greater if more than one antiepileptic used; neonatal bleeding (related to hypofibrinaemia) and neonatal hepatotoxicity also reported; *see* section 5
Vancomycin	Use only if potential benefit outweighs risk — plasma vancomycin concentration monitoring essential to reduce risk of fetal toxicity
Vecuronium	No information available; use only if potential benefit outweighs risk
Verapamil	May reduce uterine blood flow with fetal hypoxia; may inhibit labour
Vinblastine	Avoid (limited experience suggests fetal harm; teratogenic in animal studies); *see* section 8.2

Medicine	Comment
Vincristine	Avoid (teratogenicity and fetal loss in animal studies); *see* section 8.2
Warfarin	Congenital malformations; fetal and neonatal haemorrhage; *see* section 10.2
Zidovudine	Avoid if possible in first trimester; benefit of treatment considered to outweigh risk in second and third trimesters; *see* section 6.4.2.1

Appendix 3: Breastfeeding

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:

- which should be used with caution or which are contraindicated in breastfeeding for any one of the reasons given above;
- which, on present evidence, may be given to the mother during breastfeeding because they appear in milk in amounts which are too small to be harmful to the infant;
- which 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 breastfeeding. Because of the inadequacy of information on drugs in breast milk, the following table should be used only as a guide; **absence from the table does not imply safety.**

WHO POLICY. Infants should be exclusively breastfed for the first 6 months of life; thereafter they should receive appropriate complementary food and continue to be breastfed up to 2 years of age or beyond.

Advice in the table may differ from that given in other sources, including manufacturer's product literature.

For further information on use of drugs during breastfeeding, the WHO document, *Breastfeeding and maternal medication: Recommendations for drugs in the Eleventh WHO Model List of Essential Drugs.* (www.who.int/child-adolescent-health/New_Publications/NUTRITION/BF_Maternal_Medication.pdf).

Medicines present in breast milk

Medicine	Comment
Abacavir	*see* section 6.4.2
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 hypoprothrombinaemia 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
Alcohol	Large amounts may affect infant and reduce milk consumption
Alcuronium	No information available
Allopurinol	Present in milk — not known to be harmful
Amiloride	No information available; manufacturer advises avoid
Amitriptyline	Detectable in breast milk; continue breastfeeding; adverse effects possible; monitor infant for drowsiness
Amlodipine	Presence in milk possible; monitor infant
Amodiaquine	No information available
Amoxicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Amoxicillin + clavulanic acid	Trace amounts in milk
Amphotericin B	No information available
Ampicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Artemether + lumefantrine	Discontinue breastfeeding during and for 1 week after stopping treatment; present in milk in animal studies
Asparaginase	Breastfeeding contraindicated
Atenolol	Significant amounts in milk; safe in usual dosage; monitor infant
Atropine	Small amount present in milk; monitor infant

Medicine	Comment
Azathioprine	Breastfeeding contraindicated
Azithromycin	Present in milk; limited information available — use only if no suitable alternative
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 is 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
Bleomycin	Breastfeeding contraindicated
Bupivacaine	Amount too small to be harmful
Carbamazepine	Continue breastfeeding; adverse effects possible (severe skin reaction reported in one infant); monitor infant for drowsiness; *see* section 5
Cefazolin	Excreted in low concentrations; safe in usual dosage; monitor infant
Cefixime	Probably present in milk but safe in usual dosage; monitor infant
Ceftazidime	Excreted in low concentrations; safe in usual dosage; monitor infant
Ceftriaxone	Excreted in low concentrations; safe in usual dosage; monitor infant
Chlorambucil	Breastfeeding contraindicated
Chloramphenicol	Continue breastfeeding; use alternative drug if possible; may cause bone marrow toxicity in infant; concentration in milk usually insufficient to cause "grey syndrome"

Medicine	Comment
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 breastfead infant; avoid breastfeeding when used for rheumatic disease
Chlorphenamine	Safe in usual dosage; monitor infant for drowsiness
Chlorpromazine	Continue breastfeeding; adverse effects possible; monitor infant for drowsiness
Ciclosporin	Present in milk—manufacturer advises avoid
Ciprofloxacin	Continue breastfeeding; use alternative drug if possible; high concentrations in breast milk
Cisplatin	Breastfeeding contraindicated
Clindamycin	Amount probably too small to be harmful but bloody diarrhoea reported in one infant
Clofazimine	Limited information available—can cause reversible skin discoloration in nursing infant
Clomifene	May inhibit lactation
Clomipramine	Small amount present in milk; continue breastfeeding; adverse effects possible; monitor infant for drowsiness
Cloxacillin	Trace amounts in milk; safe in usual dosage; monitor infant
Codeine	Amount too small to be harmful
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)
Cyclophosphamide	Breastfeeding contraindicated during and for 36 hours after stopping treatment
Cytarabine	Breastfeeding contraindicated
Dacarbazine	Breastfeeding contraindicated
Dactinomycin	Breastfeeding contraindicated
Dapsone	Although significant amount in milk risk to infant very small; continue breastfeeding; monitor infant for jaundice

Medicine	Comment
Daunorubicin	Breastfeeding contraindicated
Deferoxamine	No information available; manufacturer advises use only if potential benefit outweighs risk
Dexamethasone	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
Diazepam	Continue breastfeeding; adverse effects possible; monitor infant for drowsiness; *see* section 5
Didanosine	*See* section 6.4.2.1
Digoxin	Amount too small to be harmful
Diloxanide	Manufacturer advises avoid
Dimercaprol	Avoid
Dopamine	No information available
Doxorubicin	Breastfeeding contraindicated
Doxycycline	Continue breastfeeding; use alternative drug if possible (absorption and therefore discoloration of teeth in infant probably usually prevented by chelation with calcium in milk)
Efavirenz	*See* section 6.4.2.2
Eflornithine	Avoid
Emtricitabine	Breastfeeding recommended during first 6 months if no safe alternative to breast milk
Enalapril	Amount probably too small to be harmful
Ephedrine	Irritability and disturbed sleep reported
Ergocalciferol	Caution with high doses; may cause hypercalcaemia in infant
Erythromycin	Only small amounts in milk—not known to be harmful
Estradiol cypionate	Avoid; adverse effects on lactation; *see also* Contraceptives, Oral
Ethambutol	Amount too small to be harmful
Ethinylestradiol	May inhibit lactation; use alternative method of contraception; *see* Contraceptives, Oral

Medicine	Comment
Ethosuximide	Significant amount in milk; continue breastfeeding; adverse effects possible; monitor infant for drowsiness; *see* section 5
Etoposide	Breastfeeding contraindicated
Fluconazole	Present in milk; safe in usual dosage; monitor infant
Flucytosine	Manufacturer advises avoid
Fluorouracil	Discontinue breastfeeding
Fluoxetine	Present in milk; manufacturer advises avoid or use lowest effective dose
Fluphenazine	Amount excreted in milk probably too small to be harmful; continue breastfeeding; adverse effects possible; monitor infant for drowsiness
Furosemide	Amount too small to be harmful
Gentamicin	Amount probably too small to be harmful; monitor infant for thrush and diarrhoea
Glibenclamide	Theoretical possibility of hypoglycaemia in infant
Griseofulvin	No information available; avoid
Haloperidol	Amount present in milk probably too small to be harmful; continue breastfeeding; 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 breastfeeding; may inhibit lactation
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
Ibuprofen	Amount too small to be harmful; short courses safe in usual doses
Imipenem + cilastatin	Present in milk; manufacturer advises avoid
Indinavir	*see* section 6.4.2.3
Insulins	Amount too small to be harmful

Medicine	Comment
Iodine	Stop breastfeeding; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk
Isoniazid	Monitor infant for possible toxicity; theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother and infant
Ivermectin	Avoid treating mother until infant is 1 week old
Lamivudine	Present in milk; *see* section 6.4.2.1
Levamisole	Breastfeeding contraindicated
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
Lithium	Present in milk and risk of toxicity in infant; continue breastfeeding; monitor infant carefully, particularly if risk of dehydration
Lopinavir + ritonavir	*See* section 6.4.2.3
Lumefantrine	*See* Artemether + Lumefantrine
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)
Mefloquine	Present in milk but risk to infant minimal
Mercaptopurine	Breastfeeding contraindicated
Metformin	Present in milk but safe in usual doses; monitor infant
Methadone	Withdrawal symptoms in infant; dose should be as low as possible and infant monitored to avoid sedation
Methotrexate	Breastfeeding contraindicated
Methyldopa	Amount too small to be harmful

Medicine	Comment
Methylthioninium chloride	No information available; avoid
Metoclopramide	Present in milk; adverse effects possible; monitor infant for adverse effects
Metronidazole	Significant amount in milk; continue breastfeeding; avoid large doses; use alternative drug if possible
Mifepristone	Avoid breastfeeding for 14 days after administration
Misoprostol	No information available; manufacturer advises avoid
Morphine	Short courses safe in usual doses; monitor infant
Naloxone	No information available
Nelfinavir	see section 6.4.2.3
Neostigmine	Amount probably too small to be harmful; monitor infant
Nevirapine	Present in milk; *see* section 6.4.2.2
Nifedipine	Small amount in milk; continue breastfeeding; monitor infant
Nitrofurantoin	Only small amounts in milk but could be enough to produce haemolysis 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)
Nystatin	No information available, but absorption from gastrointestinal tract negligible
Ofloxacin	Continue breastfeeding; use alternative drug if possible
Oxamniquine	No information available, but considered preferable to avoid
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

Medicine	Comment
Pentamidine isetionate	Manufacturer advises avoid unless essential
Pentavalent antimony compounds	Avoid
Phenobarbital	Continue breastfeeding; adverse effects possible; monitor infant for drowsiness; *see* section 5
Phenoxymethylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Phenytoin	Small amount present in milk; continue breastfeeding; adverse effects possible; monitor infant for drowsiness; *see* section 5
Polyvidone iodine	Avoid; iodine absorbed from vaginal preparations is concentrated in milk
Potassium iodide	Stop breastfeeding; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk
Praziquantel	Avoid breastfeeding during and for 72 hours after treatment; considered safe to continue breastfeeding during treatment for schistosomiasis
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 haemolysis in G6PD-deficient infants
Procainamide	Present in milk; continue breastfeeding; monitor infant
Procaine benzylpenicillin	Trace amounts in milk; safe in usual dosage; monitor infant
Procarbazine	Breastfeeding contraindicated
Proguanil	Amount in milk probably too small to be harmful at doses used for malaria prophylaxis but inadequate for reliable protection against malaria in breastfed infant
Promethazine	Safe in usual dosage; monitor infant for drowsiness
Propranolol	Present in milk; safe in usual dosage; monitor infant

Medicine	Comment
Propylthiouracil	Monitor infant's thyroid status but amounts in milk probably too small to affect infant; high doses might affect neonatal thyroid function
Pyrantel	No information available
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 breastfeeding during toxoplasmosis treatment
Quinidine	Significant amount present in milk but not known to be harmful
Quinine	Present in milk — continue breastfeeding and monitor infant; risk of haemolysis in G6PD-deficient infants
Ranitidine	Significant amount present in milk, but not known to be harmful
Retinol	Theoretical risk of toxicity in infants of mothers taking large doses
Ribavirin	Breastfeeding contraindicated
Rifampicin	Amount too small to be harmful
Ritonavir	*See* Lopinavir + ritonavir
Salbutamol	Safe in usual dosage; monitor infant
Saquinavir	*See* section 6.4.2.3
Senna	Continue breastfeeding; monitor infant for diarrhoea
Silver sulfadiazine	Continue breastfeeding; monitor infant for jaundice—small risk of kernicterus in jaundiced infants particularly with long-acting sulphonamides, and of haemolysis in G6PD-deficient infants
Simvastatin	No information available — manufacturer advises avoid
Sodium nitroprusside	No information available
Sodium valproate	*See* Valproic acid
Spectinomycin	No information available
Spironolactone	Amount probably too small to be harmful

Medicine	Comment
Stavudine	*See* section 6.4.2.1
Streptomycin	Present in milk; continue breastfeeding; monitor infant for thrush and diarrhoea
Sulfadiazine	Monitor infant for jaundice—small risk of kernicterus in jaundiced infants and of haemolysis 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 haemolysis 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 haemolysis 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 diarrhoea and rash); theoretical risk of neonatal haemolysis especially in G6PD-deficient infants; caution in ill or premature infants
Suxamethonium	No information available
Tamoxifen	Suppresses lactation; avoid unless potential benefit outweighs risk
Tenofovir	Breastfeeding recommended during first 6 months if no safe alternative to breast milk
Testosterone	Avoid; may cause masculinization in the female infant or precocious development in the male infant; high doses suppress lactation
Tetracaine	No information available
Tetracycline	Continue breastfeeding; use alternative drug if possible (absorption and therefore discoloration of teeth in infant probably usually prevented by chelation with calcium in milk)
Thiamine	Severely thiamine-deficient mothers should avoid breastfeeding as toxic methylglyoxal excreted in milk

Medicine	Comment
Thiopental	Present in milk—not known to be harmful
Trimethoprim	Present in milk; safe in usual dosage; monitor infant
Vaccine, Influenza	Not known to be harmful
Valproic acid	Amount too small to be harmful
Vancomycin	Present in milk—significant absorption following oral administration unlikely
Vecuronium	No information available
Verapamil	Amount too small to be harmful
Vinblastine	Breastfeeding contraindicated
Vincristine	Breastfeeding contraindicated
Warfarin	Risk of haemorrhage; increased by vitamin K deficiency; warfarin appears safe
Zidovudine	*See* section 6.4.2.1

Appendix 4: 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:

- **Mild**: GFR, 20–50 ml/minute or approximate serum creatinine, 150–300 micromol/litre
- **Moderate**: GFR, 10–20 ml/minute or serum creatinine, 300–700 micromol/litre

- **Severe:** GFR, <10 ml/minute or serum creatinine, >700 micromol/litre

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.
- Uraemic 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
	Moderate to severe	Reduce dose
Alcuronium	Severe	Prolonged duration of block
Allopurinol	Moderate	100–200 mg daily; increased toxicity; rash
	Severe	100 mg on alternate days (maximum 100 mg daily)

Medicine	Degree of impairment	Comment
Aluminium hydroxide	Severe	Aluminium is absorbed and may accumulate NOTE. Absorption of aluminium from aluminium salts is increased by citrates which are contained in many effervescent preparations (such as effervescent analgesics)
Amidotrizoate	Mild	Reduce dose and avoid dehydration; nephrotoxic
Amiloride	Mild	Monitor plasma potassium; high risk of hyperkalaemia in renal impairment; excreted by kidney unchanged
	Moderate	Avoid
Amoxicillin	Mild to moderate	Risk of crystalluria with high doses
	Severe	Reduce dose; rash more common and risk of crystalluria
Amoxicillin + clavulanic acid		Risk of crystalluria with high doses (particularly during parenteral therapy); reduce dose if creatinine clearance less than 30 ml/minute
Amphotericin B	Mild	Use only if no alternative; nephrotoxicity may be reduced with use of lipid formulations
Ampicillin	Severe	Reduce dose; rash more common
Artemether + Lumefantrine	Severe	Caution; monitor ECG and plasma potassium
Atenolol	Mild to moderate	Reduce dose to a maximum 50 mg daily if creatinine clearance 15–35 ml/minute
	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/minute
Azathioprine	Severe	Reduce dose
Benzathine benzylpenicillin	Severe	Neurotoxicity—high doses may cause convulsions

Medicine	Degree of impairment	Comment
Benzylpenicillin	Severe	Maximum, 6 g daily; neurotoxicity—high doses may cause convulsions
Bleomycin	Moderate	Reduce dose
Carbamazepine		Manufacturer advises caution
Cefazolin	Moderate	Reduce dose
Cefixime	Moderate	Reduce dose
Ceftazidime	Mild	Reduce dose
Ceftriaxone	Severe	Maximum, 2 g daily; also monitor plasma concentration if both severe renal impairment and hepatic impairment
Chlorambucil	Moderate	Use with caution and monitor response; increased risk of myelosuppression
Chloramphenicol	Severe	Avoid unless no alternative; dose-related depression of haematopoiesis
Chloroquine	Mild to moderate	Reduce dose in rheumatic disease
	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
Ciclosporin		Monitor kidney function—dose-dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction (exclude rejection if kidney transplant)
Ciprofloxacin	Moderate	Use half normal dose
Cisplatin	Mild	Avoid if possible; nephrotoxic and neurotoxic
Clindamycin		Plasma half-life prolonged—may need dose reduction
Cloxacillin	Severe	Reduce dose
Codeine	Moderate to severe	Reduce dose or avoid; increased and prolonged effect; increased cerebral

Medicine	Degree of impairment	Comment
		sensitivity
Cyclophosphamide		Reduce dose
Dacarbazine	Mild to moderate	Dose reduction may be required
	Severe	Avoid
Daunorubicin	Mild to moderate	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
Didanosine	Mild	Reduce dose; consult manufacturer's literature
Diethylcarbamazine	Moderate to severe	Reduce dose; plasma half-life prolonged and urinary excretion considerably reduced
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
Eflornithine		Reduce dose
Emtricitabine	Mild	Reduce dose; consult manufacturer's literature
Enalapril	Mild	Use with caution and monitor response; initial dose, 2.5 mg once daily if creatinine clearance less than 30 ml/minute; hyperkalaemia and other adverse effects more common
Ephedrine	Severe	Avoid; increased CNS toxicity
Ergometrine	Severe	Manufacturer advises avoid
Erythromycin	Severe	Maximum, 1.5 g daily (ototoxicity)

Medicine	Degree of impairment	Comment
Ethambutol	Mild	Reduce dose; if creatinine clearance less than 30 ml/minute monitor plasma ethambutol concentration; optic nerve damage
Etoposide		Consider dose reduction
Fluconazole	Mild to moderate	Usual initial dose then halve subsequent doses
Flucytosine		Reduce dose and monitor plasma flucytosine concentration; consult manufacturer's literature
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; *see* section 6.2.2
Glibenclamide	Severe	Avoid
Haloperidol	Severe	Start with small doses; increased cerebral sensitivity
Heparin	Severe	Risk of bleeding increased
Hydralazine	Mild	Reduce dose if creatinine clearance less than 30 ml/minute
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
	Moderate to severe	Avoid
Imipenem + cilastatin	Mild	Reduce dose
Insulins	Severe	May need dose reduction; insulin requirements fall; compensatory response to hypoglycaemia is impaired
Iohexol	Moderate to severe	Increased risk of nephrotoxicity; avoid dehydration

Appendix 4: Renal impairment

Medicine	Degree of impairment	Comment
Isoniazid	Severe	Maximum, 200 mg daily; peripheral neuropathy
Lamivudine	Mild	Reduce dose; consult manufacturer's literature
Lidocaine	Severe	Caution
Lithium	Mild	Avoid if possible or reduce dose and monitor plasma concentration carefully
	Moderate	Avoid
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
Meglumine antimoniate		*See* Pentavalent antimony compounds
Meglumine iotroxate	Moderate to severe	Increased risk of nephrotoxicity; avoid dehydration
Mercaptopurine	Moderate	Reduce dose
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
	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
Morphine	Moderate to severe	Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity

Medicine	Degree of impairment	Comment
Nelfinavir		No information available; manufacturer advises caution
Neostigmine	Moderate	May need dose reduction
Nitrofurantoin	Mild	Avoid; peripheral neuropathy; ineffective because of inadequate urine concentrations
Paromomycin	Mild	Avoid
Penicillamine	Mild	Reduce dose and monitor renal function
	Moderate to severe	Avoid
Pentamidine isetionate	Mild	Reduce dose; consult manufacturer's literature
Pentavalent antimony compounds	Moderate	Increased adverse effects
	Severe	Avoid
Phenobarbital	Severe	Avoid large doses
Polyvidone iodine	Severe	Avoid regular application to inflamed or broken mucosa
Potassium chloride	Moderate	Avoid routine use; high risk of hyperkalaemia
Procainamide	Mild	Avoid or reduce dose
Procaine benzylpenicillin	Severe	Neurotoxicity—high doses may cause convulsions
Procarbazine	Severe	Avoid
Proguanil	Mild	100 mg once daily
	Moderate	50 mg on alternate days
	Severe	50 mg once weekly; increased risk of haematological toxicity
Propranolol	Severe	Start with small dose; higher plasma concentrations after oral administration; may reduce renal blood flow and adversely affect renal function
Propylthiouracil	Mild to moderate	Use three quarters normal dose

Medicine	Degree of impairment	Comment
	Severe	Use half normal dose
Pyridostigmine	Moderate	Reduce dose; excreted by kidney
Pyrimethamine		Use with caution
Quinine		Reduce parenteral maintenance dose for malaria treatment
Ranitidine	Severe	Use half normal dose; occasional risk of confusion
Ribavirin	Mild	Plasma ribavirin concentration increased; avoid if creatinine clearance less than 30 ml/minute; monitor haemoglobin concentration carefully
Ritonavir		*See* Lopinavir + ritonavir
Saquinavir	Severe	Dose adjustment possibly required
Simvastatin	Mild	Use doses above 10 mg daily with caution if creatinine clearance less than 30 ml/minute
Sodium chloride	Severe	Avoid
Sodium hydrogen carbonate	Severe	Avoid; specialized role in some forms of renal disease
Sodium nitroprusside	Moderate	Avoid prolonged use
Sodium valproate		*See* Valproic acid
Spironolactone	Mild	Monitor plasma potassium concentrations; high risk of hyperkalaemia in renal impairment
	Moderate	Avoid
Stavudine	Mild	20 mg twice daily (15 mg if body weight less than 60 kg)
	Moderate to severe	20 mg once daily (15 mg if body weight less than 60 kg)
Streptomycin	Mild	Reduce dose; monitor plasma concentrations
Sulfadiazine	Severe	Avoid; high risk of crystalluria

Medicine	Degree of impairment	Comment
Sulfamethoxazole + trimethoprim	Mild	Use half normal dose if creatinine clearance 15–30 ml/minute; avoid if creatinine clearance less than 15 ml/minute and if plasma sulfamethoxazole concentration cannot be monitored
Sulfasalazine	Moderate	Risk of toxicity including crystalluria—ensure high fluid intake
	Severe	Avoid
Tenofovir	Mild	Increase dose interval; consult manufacturer's literature
Trimethoprim	Mild	Use half normal dose after 3 days if creatinine clearance 15–30 ml/minute
	Moderate to severe	Use half normal dose if creatinine clearance less than 15 ml/minute; avoid if creatinine clearance less than 10 ml/minute (unless plasma trimethoprim concentration monitored)
Valproic acid	Mild to moderate	Reduce dose
	Severe	Alter dosage according to free serum valproic acid concentration
Vancomycin	Mild	Reduce dose; monitor plasma vancomycin concentration and renal function regularly
Warfarin	Severe	Avoid
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 5: 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, oedema) 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). *Oedema* 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 help prescribing in hepatic impairment is included in the following table. The table contains only those drugs that need dose adjustment. However, absence from 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
Alcuronium	Possibly slower onset, higher dose requirement and prolonged recovery time
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)
Amidotrizoate	Use with caution in severe hepatic impairment
Amitriptyline	Sedative effect increased (avoid in severe liver disease)
Amlodipine	Half-life prolonged — may need dose reduction; consider initial dose of 2.5 mg
Amodiaquine	Avoid
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
Artemether + lumefantrine	Caution in severe impairment — monitor ECG and plasma potassium
Azathioprine	May need dose reduction
Azithromycin	Avoid; jaundice reported
Bupivacaine	Avoid (or reduce dose) in severe liver disease

Appendix 5: Hepatic impairment

Medicine	Comment
Carbamazepine	Metabolism impaired in advanced liver disease
Ceftriaxone	Reduce dose and monitor plasma concentration if both hepatic and severe renal impairment
Chlorambucil	Limited information available — consider dose reduction in severe hepatic 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
Ciclosporin	May need dose adjustment
Clindamycin	Reduce dose
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
Codeine	Avoid or reduce dose — may precipitate coma
Contraceptives, Oral	Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy
Cyclophosphamide	Reduce dose
Cytarabine	Reduce dose
Dacarbazine	Dose reduction may be required in mild to moderate liver disease; avoid if severe
Daunorubicin	Reduce dose
Diazepam	Can precipitate coma
Didanosine	Insufficient information but monitor for toxicity
Doxorubicin	Reduce dose according to bilirubin concentration
Doxycycline	Avoid (or use with caution)

Medicine	Comment
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
Ergometrine	Avoid in severe liver disease
Erythromycin	May cause idiosyncratic hepatotoxicity
Estradiol cypionate	Avoid; *see also* Contraceptives, Oral
Ethinylestradiol	Avoid; *see also* Contraceptives, Oral
Etoposide	Avoid in severe hepatic impairment
Fluconazole	Toxicity with related drugs
Fluorouracil	Caution advised; dose reduction may be required
Fluoxetine	Reduce dose or administer on alternate days
Fluphenazine	Can precipitate coma; hepatotoxic
Furosemide	Hypokalaemia may precipitate coma (use potassium-sparing diuretic to prevent this); increased risk of hypomagnesaemia in alcoholic cirrhosis
Glibenclamide	Increased risk of hypoglycaemia 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; hypokalaemia may precipitate coma (potassium-sparing diuretic can prevent this); increased risk of hypomagnesaemia in alcoholic cirrhosis

Medicine	Comment
Ibuprofen	Increased risk of gastrointestinal bleeding and can cause fluid retention; avoid 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 impairment
Isoniazid	Use with caution; monitor liver function regularly and particularly frequently in the first 2 months; *see* section 6.2.4
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
Medroxyprogesterone acetate	Avoid in active liver disease and if history of pruritus during pregnancy
Mefloquine	Avoid for prophylaxis in severe liver disease
Meglumine antimoniate	*See* Pentavalent antimony compounds
Mercaptopurine	May need dose reduction
Metformin	Withdraw if tissue hypoxia likely—manufacturers advise 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
Metoclopramide	Reduce dose
Metronidazole	In severe liver disease, reduce total daily dose to one third and give once daily

Medicine	Comment
Morphine	Avoid or reduce dose—may precipitate coma
Nelfinavir	No information available; manufacturer advises caution
Nevirapine	Caution in moderate hepatic impairment; avoid in severe hepatic impairment; *see* section 6.4.2.2
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
Ofloxacin	Hepatic dysfunction reported; reduce dose in severe liver disease
Paracetamol	Dose-related toxicity—avoid large doses
Pentavalent antimony compounds	Increased risk of liver damage and hepatic failure in pre-existing liver disease
Phenobarbital	May precipitate coma
Phenytoin	Reduce dose to avoid toxicity
Prednisolone	Adverse effects more common
Procainamide	Avoid or reduce dose
Procarbazine	Avoid in severe hepatic impairment
Promethazine	Avoid—may precipitate coma in severe liver disease; hepatotoxic
Propranolol	Reduce oral dose
Propylthiouracil	Reduce dose; *see* section 18.8
Pyrazinamide	Monitor hepatic function—idiosyncratic hepatotoxicity more common; avoid in severe hepatic impairment; *see* section 6.2.4
Pyrimethamine	Use with caution
Ranitidine	Increased risk of confusion; reduce dose
Ribavirin	Avoid in severe hepatic dysfunction or decompensated cirrhosis

Medicine	Comment
Rifampicin	Impaired elimination; monitor liver function; avoid or do not exceed 8 mg/kg daily; *see* section 6.2.4
Ritonavir	*See* Lopinavir + ritonavir
Saquinavir	Manufacturer advises caution in moderate hepatic impairment; avoid in severe impairment
Simvastatin	Avoid in active liver disease or unexplained persistent elevations in serum transaminases
Sodium nitroprusside	Avoid in severe liver disease
Sodium valproate	*See* Valproic acid
Sulfadiazine	Avoid if severe
Sulfamethoxazole + trimethoprim	Manufacturer advises avoid in severe liver disease
Suxamethonium	Prolonged apnoea may occur in severe liver disease due to reduced hepatic synthesis of plasma cholinesterase
Testosterone	Preferably avoid—possibility of dose-related toxicity and fluid retention
Thiopental	Reduce dose for induction in severe liver disease
Valproic acid	Avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months)
Verapamil	Reduce oral dose
Vinblastine	Dose reduction may be necessary
Vincristine	Dose reduction may be necessary
Warfarin	Avoid in severe liver disease, especially if prothrombin time already prolonged
Zidovudine	Accumulation may occur

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