Anti-infective drugs

Anthelminthics

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

In *animal* studies, albendazole and mebendazole have been found to be teratogenic. They are contraindicated for the treatment of cestode infections in pregnancy; pregnancy should be excluded before treatment with albendazole (non-hormonal contraception during and for 1 month after treatment). For single-dose or short-term use in pregnancy, see section 6.1.1.2.

HYMENOLEPIASIS

In hymenolepiasis, **praziquantel** is 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. It thus offers the prospect of a cure for neurocysticercosis, which has been treatable only by surgery, anti-inflammatory

corticosteroids and anticonvulsants. 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. 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.

Albendazole

Chewable tablets, albendazole 400 mg

Uses:

Echinococcus multilocularis and *E. granulosus* infections prior to or not amenable to surgery; neurocysticercosis; nematode infections (sections 6.1.1.2 and 6.1.1.3); filariasis (section 6.1.2.2)

Contraindications:

pregnancy (Appendix 2; see notes above and Precautions)

Precautions:

liver function tests and blood counts before treatment and twice during each cycle; exclude pregnancy before starting treatment (non-hormonal contraception during and for 1 month after treatment); breastfeeding; **interactions:** Appendix 1

Dosage:

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 two divided doses (to a maximum daily dose of 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 two divided doses (to a maximum daily dose of 800 mg) for 8–30 days

Adverse effects:

gastrointestinal disturbances, headache, dizziness; increases in liver enzymes; reversible alopecia; rash; fever; leukopenia and rarely, pancytopenia; allergic shock if cyst leakage; convulsions and meningism in cerebral disease

Mebendazole

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

Chewable tablets, mebendazole 100 mg, 500 mg

Uses:

Echinococcus granulosus and *E. multilocularis* infections before surgery or not amenable to surgery; nematode infections (sections 6.1.1.2 and 6.1.1.3)

Contraindications:

pregnancy (Appendix 2; see also notes above)

Precautions:

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

Dosage:

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

Patient Advice. Doses should be taken between meals

Adverse effects:

gastrointestinal disturbances, headache, dizziness; with high doses, allergic reactions, raised liver enzymes, alopecia, bone marrow depression

Niclosamide

Chewable tablets, niclosamide 500 mg

Uses:

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)

Dosage:

Taenia solium infection, *by mouth* , **ADULT** and **CHILD** over 6 years 2 g as a single dose after a light breakfast, followed by a purgative after 2 hours; **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 purgative 2 hours after last dose

Hymenolepis nana infection, *by mouth* , **ADULT** and **CHILD** over 6 years 2 g as a single dose on 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, 2–6 years, 1 g on 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

Tablets, praziquantel 150 mg, 600 mg

Uses:

Taenia saginata, T. solium, Hymenolepis nana and *Diphyllobothrium latum* infections; trematode infections (sections 6.1.3.1 and 6.1.3.2)

Contraindications:

ocular cysticercosis

Precautions:

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

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

Dosage:

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 infection, *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, eosinophilia (may be due to dead and dying parasites); in neurocysticercosis, headache, hyperthermia, seizures, intracranial hypertension (inflammatory response to dead and dying parasites in CNS)

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 **mebendazole** or **albendazole** 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 **mebendazole** , **albendazole** or **pyrantel** . Since reinfection readily occurs, at least one further dose should be given 2–4 weeks later. Piperazine is also effective but must be taken regularly for at least 7 consecutive days.

HOOKWORM INFECTIONS

Hookworm infections are caused by *Ancylostoma duodenale* (ancylostomiasis) and *Necator americanus* (necatoriasis); they are a major cause of iron-deficiency 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 second- and third-trimester of pregnancy, children and debilitated patients. In

hookworm, broad-spectrum anthelminthics are preferred wherever other nematode infections are endemic. Both **mebendazole** and **albendazole** are effective.

In *animal* studies, **albendazole** and **mebendazole** have been found to be teratogenic. 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. However, 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 section 6.1.1.1).

Levamisole is effective in the treatment of mixed *Ascaris* and hookworm infections and **pyrantel** has been highly effective 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 daily for adults) for at least 3 months after the haemoglobin concentration of 12 g/100 ml is obtained.

STRONGYLOIDIASIS

Strongyloidiasis is an infection of the small intestine caused by *Strongyloides stercoralis* . All infected patients should be treated. **Ivermectin** in a single dose of 200 micrograms/kg or 200 micrograms/kg/day on two 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 it 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.

Albendazole

Chewable tablets, albendazole 400 mg

Uses:

ascariasis, hookworm infections, strongyloidiasis, enterobiasis, trichuriasis, trichostrongyliasis, and capillariasis; cestode infections (section 6.1.1.1); tissue nematode infections (section 6.1.1.3); filariasis (6.1.2.2)

Precautions:

pregnancy (see notes above and Appendix 2; also section 6.1.1.1); **interactions:** Appendix 1

Dosage:

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 discomfort, headache; adverse effects associated with use in cestode infections (section 6.1.1.1)

Levamisole

Tablets , levamisole (as hydrochloride) 40 mg, 50 mg, 150 mg

Uses:

ascariasis, hookworm, and mixed ascariasis with hookworm infections; malignant disease (section 8.2)

Contraindications:

breastfeeding (Appendix 3)

Precautions:

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

Dosage:

Ascariasis, hookworm, 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, and headache

Mebendazole

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

Chewable tablets, mebendazole 100 mg, 500 mg

Uses:

ascariasis, hookworm infections, enterobiasis, trichuriasis, and capillariasis; cestode infections (section 6.1.1.1); tissue nematode infections (section 6.1.1.3)

Precautions:

pregnancy (Appendix 2; see also notes above and section 6.1.1.1); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

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, and dizziness; adverse effects associated with use in cestode infections (section 6.1.1.1)

Pyrantel

Chewable tablet, pyrantel (as embonate) 250 mg

Oral suspension, pyrantel (as embonate) 50 mg/ml

Uses:

ascariasis, hookworm infections, enterobiasis, and trichostrongyliasis; tissue nematode infections (section 6.1.1.3)

Precautions:

pregnancy; breastfeeding; liver disease (reduce dose)

Dosage:

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

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 salt-water fish; and 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** (section 6.1.1) 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 6.4.1) (25 mg/kg daily for 10 days, with 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** (section 6.1.1) (200 mg daily for 5 days), **albendazole** (section 6.1.1) (400 mg daily for 3 days), and **pyrantel** (section 6.1.1) (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.

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.

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 as 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 dosage and corticosteroid and antihistamine cover should be provided for the first 2 to 3 days.

Diethylcarbamazine citrate

Diethylcarbamazine citrate is a complementary antifilarial drug

Tablets, diethylcarbamazine citrate 50 mg, 100 mg

Uses:

treatment of loiasis; prophylaxis of loiasis in temporary residents in endemic areas; tissue nematode infections (section 6.1.1.3); lymphatic filariasis (section 6.1.2.2)

Contraindications:

pregnancy (delay treatment until after delivery); infants, elderly, debilitated (usually excluded from mass treatment programmes; see also Precautions)

Precautions:

renal impairment (reduce dose; Appendix 4); cardiac disorders; other severe acute diseases—delay diethylcarbamazine treatment until after recovery; risk of meningoencephalitis in severe infection (see notes above)

Dosage:

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 mimimize 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, and including fever, headache, joint pain, dizziness, anorexia, malaise, nausea and vomiting, urticaria, and asthma in asthmatics (similar to Mazzotti reaction—see section 6.1.2.3),

induced by disintegrating microfilariae; microencephalitis (with heavy microfilaraemia, see notes above); reversible proteinuria

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 *Wuchereria bancrofti* infections with half this dose used for *Brugia 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 is continued for at least 5 years. Trials in India and China have shown that the consistent use for 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.

Diethylcarbamazine citrate

Diethylcarbamazine citrate is a complementary antifilarial drug

Tablets , diethylcarbamazine citrate 50 mg, 100 mg

Uses:

systemic lymphatic filariasis and occult filariasis; loiasis (section 6.1.2.1); tissue nematode infections (section 6.1.1.3)

Contraindications:

pregnancy (delay treatment until after delivery)

Precautions:

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

Dosage:

Lymphatic filariasis (bancroftian), *by mouth* , **ADULT** and **CHILD** over 10 years, 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, 3–6 mg/kg, 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

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, asthma in asthmatics (similar to Mazzotti reaction—see section 6.1.2.3) induced by disintegrating microfilariae; nodules (palpable subcutaneously and along spermatic cord—formed by recently killed worms); transient lymphangitis and exacerbation of lymphoedema

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. Its microfilaricidal action is more persistent and less liable to provoke adverse reactions than that of diethylcarbamazine. A single oral dose 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 the microfilaraemia to a degree that prevents development of clinical disease. Although the drug is generally well tolerated, it is advisable to have medical support available during treatment programmes. Patients with a heavy microfilarial load occasionally react adversely and, 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 is now largely superseded as a microfilaricide in onchocerciasis because of the frequency with which it induces severe host (Mazzotti) reactions characterized by itching, rash, oedema, pain and swelling of the lymph nodes, fever and severe eye lesions.

Suramin 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.

Ivermectin

Tablets, ivermectin 3 mg, 6 mg

Uses:

suppressive treatment of onchocerciasis; filariasis (section 6.1.2.2)

Contraindications:

pregnancy (delay treatment until after delivery)

Precautions:

breastfeeding (avoid treating mother until infant is 1 week old)

Dosage:

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—fever, headache, sore throat, cough, pruritus, rash, conjunctivitis, arthralgia, myalgia, lymphadenopathy, lymphadenitis, oedema, weakness, tachycardia, nausea and vomiting, diarrhoea

Suramin sodium

Suramin sodium is a complementary drug

Injection (Powder for solution for injection), suramin sodium 1-g vial

Uses:

curative treatment of onchocerciasis; trypanosomiasis (section 6.4.4.1)

Contraindications:

previous anaphylaxis or suramin sensitivity; pregnancy (delay treatment until after delivery); severe liver or renal function impairment; 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 notes above); first dose—possible loss of consciousness (see under Dosage, 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

Dosage:

Curative treatment of onchocerciasis, *by slow intravenous injection* , **ADULT** 3.3 mg/kg as a single dose (see First (Test) Dose administration, 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 First (Test) Dose, 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

Trematode 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.

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 lack of information on whether oxamniquine is excreted in breast milk, it is preferable not to administer it to nursing mothers.

Oxamniquine

Oxamniquine is a complementary drug

Capsules, oxamniquine 250 mg

Oral suspension, oxamniquine 250 mg/5 ml

Uses:

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

Precautions:

epilepsy—close observation, may precipitate seizures; pregnancy and breastfeeding (see notes above)

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

Dosage:

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, epileptiform convulsions; raised liver enzyme values; transient fever, eosinophilia, scattered pulmonary infiltrates (Loeffler syndrome)—after 3-day course in patients in Egypt and eastern Mediterranean

Praziquantel

Tablets , praziquantel 600 mg

Uses:

intestinal schistosomiasis; urinary schistosomiasis; cestode infections (section 6.1.1.1); fluke infections (section 6.1.3.2)

Contraindications:

ocular cysticercosis (see section 6.1.1.1)

Precautions:

pregnancy (Appendix 2); 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, driving

Dosage:

Schistosomiasis, *by mouth* , **ADULT** and **CHILD** over 4 years 40–60 mg/kg as a single dose; alternatively 3 doses of 20 mg/kg on one day at intervals of 4–6 hours

Adverse effects:

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

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.

Praziquantel

Tablets , praziquantel 600 mg

Uses:

intestinal flukes, liver flukes, and lung flukes; cestode infections (section 6.1.1.1); schistosomiasis (section 6.1.3.1)

Contraindications:

ocular cysticercosis (see section 6.1.1.1)

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); areas endemic for cysticercosis—possible oedematous reaction; **interactions:** Appendix 1

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

Dosage:

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

Adverse effects:

abdominal discomfort, nausea, vomiting, malaise, headache, dizziness, drowsiness, rectal bleeding; rarely hypersensitivity reactions, including fever, pruritus

Triclabendazole

Tablets, triclabendazole 250 mg

Uses:

fascioliasis; paragonimiasis

Precautions:

Paragonimus infections—treatment in hospital as may be central nervous system involvement; severe fascioliasis—biliary colic, due to obstruction by dying worms

Dosage:

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 given in 2 divided doses

Adverse effects:

gastrointestinal discomfort; headache

Antibacterials

Beta-lactam drugs

Beta-lactam antibiotics including 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 having Gram-positive and some Gram-negative activity; the second generation drugs have improved Gram-negative activity and the third generation cefalosporins have a wider spectrum of activity, although may be less active against Gram-positive bacteria than first generation drugs, but they are active against Gram-negative Enterobacteriaceae and *Pseudomonas aeruginosa* .

Carbapenems are semisynthetic derivatives of *Streptomyces cattleya* . They have a broad spectrum of activity and are stable to most penicillinases. They should be reserved for severe infections resistant to other antibiotics.

Penicillins may cause encephalopathy due to cerebral irritation. This rare, but serious adverse effect may result from very high doses or in 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 rashes 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 penicllin administration are at risk of immediate hypersensitivity to a penicillin. These individuals should not receive a penicillin, a cefalosporin or another beta-lactam antibiotic. Patients who are allergic to one penicillin will be allergic to them all because the hypersensitivity is related to the basic penicillin structure and 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 penicillin and benzylpenicillin is 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. **Benzathine benzylpenicillin** or **procaine benzylpenicillin** provides a tissue depot from which the drug 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 but is less effective than benzylpenicillin. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable.

Benzylpenicillin

Penicillin G

Injection (Powder for solution for injection), benzylpenicillin sodium 600-mg vial (1 million units), 3-g vial (5 million units)

Uses:

pneumonia; throat infections; otitis media; Lyme disease in children; streptococcal endocarditis; meningococcal disease; necrotizing enterocolitis; necrotizing fasciitis; leptospirosis; neurosyphilis; anthrax; actinomycosis; brain abscess; gas gangrene; cellulitis; osteomyelitis

Contraindications:

penicillin hypersensitivity (see notes above); avoid intrathecal route (see notes above)

Precautions:

history of allergy (see notes above); renal failure (Appendix 4); heart failure; pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

Dosage:

Mild to moderate infections due to sensitive organisms, *by intramuscular injection or by slow intravenous injection or by intravenous infusion* , **ADULT** 0.6–2.4 g daily in 2–4 divided doses, with higher doses in severe infections and duration of treatment depending on disease (see also below); **neonate** 50 mg/kg daily in 2 divided doses; **infant** 1 to 4 weeks, 75 mg/kg daily in 3 divided doses; **CHILD** 1 month to 12 years, 100 mg/kg daily in 4 divided doses, with higher doses in severe infections (see also below)

Bacterial endocarditis, *by slow intravenous injection or by intravenous infusion* , **ADULT** up to 7.2 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** 100 mg/kg daily in 2 divided doses; **infant** 150 mg/kg daily in 3 divided doses; **CHILD** 1 month to 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; **CHILD** under 1 year, 300 mg; **CHILD** 1 to 9 years, 600 mg

Neurosyphilis, *by slow intravenous injection* , **ADULT** 1.8–2.4 g every 4 hours for 2 weeks

Congenital syphilis, *by intramuscular injection or by slow intravenous injection* , **CHILD** up to 2 years, 30 mg/kg daily in 2 divided doses for 10 days; **CHILD** over 2 years, 120–180 mg/kg (to a maximum of 1.44 g) daily in divided doses for 14 days

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects:

hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis (see also 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

Benzathine benzylpenicillin

Injection (Powder for solution for injection), benzathine benzylpenicillin, 1.8-g vial (equivalent to benzylpenicillin 1.44 g, 2.4 million units)

Uses:

streptococcal pharyngitis; diphtheria carrier state; syphilis and other treponemal infections (yaws, pinta, bejel); rheumatic fever prophylaxis

Contraindications:

penicillin hypersensitivity (see notes above); intravascular injection; neurosyphilis

Precautions:

history of allergy (see notes above); renal failure (Appendix 4); pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

Dosage:

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 two 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, and 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, rashes, angioedema, anaphylaxis, serum sickness-like reaction, haemolytic anaemia, interstitial nephritis (see also notes above); neutropenia, thrombocytopenia, coagulation disorders and 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

Procaine benzylpenicillin

Injection (Powder for solution for injection), procaine benzylpenicillin 1-g vial (1 million units), 3-g vial (3 million units)

Uses:

syphilis; anthrax; childhood pneumonia; diphtheria carrier state; cellulitis; mouth infections; bites

Contraindications:

hypersensitivity to penicillins (see notes above); intravascular injection

Precautions:

history of allergy (see notes above); renal failure (Appendix 4); **interactions:** Appendix 1

Dosage:

Infections due to sensitive organisms, *by deep intramuscular injection* , **ADULT** 0.6 to 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 to 15 days, or up to 3 weeks in late syphilis

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, rashes, angioedema, anaphylaxis, serum sickness-like reaction, haemolytic anaemia, interstitial nephritis (see also notes 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

Phenoxymethylpenicillin

Penicillin V

Tablets, phenoxymethylpenicillin (as potassium salt) 250 mg

Oral suspension (Powder for oral suspension)*,* phenoxymethylpenicillin (as potassium salt) 250 mg/5 ml

Uses:

streptococcal pharyngitis; otitis media; erysipelas; mouth infections; secondary prophylaxis of rheumatic fever; post-splenectomy prophylaxis

Contraindications:

hypersensitivity to penicillins (see notes above); serious infections (see notes above)

Precautions:

history of allergy (see notes above); pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

Dosage:

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, anaphylaxis (see notes above); nausea and diarrhoea

Ampicillin, amoxicillin, amoxicillin with clavulanic acid and cloxacillin

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 is important. In some areas, oral use should be restricted to treatment of *Shigella* infections; it is given in an oral dose of 1 g every 6 hours for 7–10 days.

Amoxicillin has a similar spectrum of activity to ampicillin, but 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.

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, genito-urinary 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 spectrums of activity. The penicillin and aminoglycoside should not be mixed before or during administration, because loss of aminoglycoside activity can occur on mixing.

Amoxicillin

Capsules, amoxicillin 250 mg, 500 mg

Oral suspension (Powder for oral suspension), amoxicillin 125 mg/5 ml

Uses:

urinary-tract infections, upper respiratory-tract infections, bronchitis; pneumonia; otitis media; dental abscess; osteomyelitis; Lyme disease in children; endocarditis prophylaxis; post-splenectomy prophylaxis; gynaecological infections; gonorrhoea; *Helicobacter pylori* eradication (section 17.1)

Contraindications:

hypersensitivity to penicillins (see notes above)

Precautions:

history of allergy (see notes above); renal impairment (Appendix 4); erythematous rashes common in glandular fever, chronic lymphatic leukaemia, and possibly HIV infection; pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

Dosage:

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

Chlamydia, *by mouth* , 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 (short course), *by mouth* , **CHILD** aged 3–10 years, 750 mg twice daily for 2 days

Adverse effects:

nausea and vomiting, diarrhoea; rashes (hypersensitivity or toxic response; may be serious reaction—discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis (see also notes 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 with clavulanic acid

Tablets , amoxicillin (as trihydrate) 500 mg with clavulanic acid (as potassium salt) 125 mg

Oral suspension (Powder for oral suspension), amoxicillin (as trihydrate) 125 mg with clavulanic acid (as potassium salt) 31 mg [not included on WHO Model List]

Oral suspension (Powder for oral suspension), amoxicillin (as trihydrate) 250 mg with clavulanic acid (as potassium salt) 62 mg [not included on WHO Model List]

Injection (Powder for solution for injection), amoxicillin (as sodium salt) 0.5 g or 1 g with clavulanic acid (as potassium salt) 100 mg or 200 mg respectively [not included on WHO Model List]

Uses:

infections due to beta-lactamase producing bacteria (where amoxicillin alone not appropriate) including respiratory-tract infections, genito-urinary and abdominal infections, cellulitis, animal bites, severe dental infections, and surgical prophylaxis

Contraindications:

hypersensitivity to penicillins (see notes above); history of penicillin- or amoxicillin with clavulanic acid-associated jaundice or hepatic dysfunction

Precautions:

history of allergy (see notes above); renal impairment (Appendix 4); erythematous rashes common in glandular fever, chronic lymphatic leukaemia, and possibly HIV infection; hepatic impairment (Appendix 5); pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

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; 1–6 years, 125 mg every 8 hours; 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; rashes (hypersensitivity or toxic response—may be serious, discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-type reaction, haemolytic anaemia, interstitial nephritis (see also notes above); rarely, antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders; dizziness, headache, convulsions (particularly with high doses or in renal impairment); hepatitis, cholestatic jaundice; erythema multiforme (including Stevens-Johnson syndrome), toxic epidermal necrolysis, exfoliative dermatitis, vasculitis reported; superficial staining of teeth with suspension; phlebitis at injection site

Ampicillin

Injection (Powder for solution for injection), ampicillin (as sodium salt) 500-mg vial, 1-g vial

Uses:

mastoiditis; gynaecological infections; septicaemia; peritonitis; endocarditis; meningitis; cholecystitis; osteomyelitis

Contraindications:

hypersensitivity to penicillins (see notes above)

Precautions:

history of allergy (see notes above); renal impairment (Appendix 4); erythematous rashes common in glandular fever, acute or chronic lymphocytic leukaemia, and cytomegalovirus infection; pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

Dosage:

Severe infections due to sensitive organisms, *by intramuscular* , *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** 2 g every 4 hours for 10–14 days; **infant** under 1 month, 50 mg/kg every 6 hours; 1–3 months, 50–100 mg/kg every 6 hours; **child** 3 months–12 years, 100 mg/kg every 6 hours (maximum 12 g daily)

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects:

nausea and vomiting, diarrhoea; rashes (hypersensitivity or toxic response—may be serious reaction, discontinue treatment); hypersensitivity reactions including urticaria, angioedema, anaphylaxis, serum sickness-like reaction, haemolytic anaemia, interstitial nephritis (see also notes above); rarely, antibiotic-associated colitis; neutropenia, thrombocytopenia, coagulation disorders

Cloxacillin

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

Capsules , cloxacillin (as sodium salt) 500 mg

Oral solution (Powder for oral solution), cloxacillin (as sodium salt) 125 mg/5 ml

Injection (Powder for solution for injection), cloxacillin (as sodium salt) 500-mg vial

Uses:

infections due to beta-lactamase-producing staphylococci including impetigo, cellulitis and other soft-tissue infections; staphylococcal endocarditis, septicaemia, pneumonia and osteomyelitis

Contraindications:

hypersensitivity to penicillins (see notes above)

Precautions:

history of allergy (see notes above); renal and hepatic impairment (Appendices 4 and 5); heart failure; pregnancy and breastfeeding (Appendices 2 and 3); **interactions:** Appendix 1

Dosage:

Infections due to susceptible beta-lactamase-producing staphylococci, *by mouth* , **ADULT** 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 intravenous infusion* , 1–2 g every 6 hours; **CHILD** up to 2 years, quarter adult dose; **CHILD** 2–10 years, half adult dose

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects:

nausea and vomiting, diarrhoea; hypersensitivity reactions including urticaria, fever, joint pain, rashes, angioedema, anaphylaxis, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis (see also notes above); neutropenia, thrombocytopenia, coagulation disorders; antibiotic-associated colitis; hepatitis and cholestatic

jaundice—may be delayed in onset; electrolyte disturbances; pain, inflammation, phlebitis or thrombophlebitis at injection sites

Cefalosporins and imipenem with cilastatin

Ceftazidime and **ceftriaxone** are third generation cefalosporins. 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 and in some areas is restricted to use only where gentamicin resistance is high.

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 reserve agent for the treatment of infections due to *Acinetobacter* spp. and *Ps aeruginosa,* which are resistant to other more usual treatments.

Ceftazidime

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

Injection (Powder for solution for injection), ceftazidime (as pentahydrate) 250-mg vial

Uses:

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

Contraindications:

cefalosporin hypersensitivity (see section 6.2.1); porphyria

Precautions:

penicillin sensitivity (see section 6.2.1); renal impairment (Appendix 4); 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

Dosage:

Infections due to susceptible organisms, *by deep intramuscular injection or by intravenous injection or intravenous infusion* , **ADULT** 1 g every 8 hours *or* 2 g every 12 hours, or in severe infections (including immunocompromised), 2 g every 8–12 hours *or* 3 g every 12 hours (**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 or by intravenous injection or intravenous infusion* , **ADULT** with normal renal function, 100–150 mg/kg daily in 3 divided doses

Infections in 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 divided between more than one site

Adverse effects:

diarrhoea, nausea, vomiting, abdominal discomfort, headache; rarely, antibiotic-associated colitis (particularly with higher doses); allergic reactions including rashes, pruritus, urticaria, serum sickness-like reaction, fever and arthralgia, and anaphylaxis; erythema multiforme, 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

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

Ceftriaxone is a complementary antibacterial drug for use only when there is significant resistance to other drugs on the WHO Model List

Injection (Powder for solution for injection), ceftriaxone (as sodium salt) 250-mg vial

Uses:

serious infections due to sensitive bacteria, including septicaemia, pneumonia, and meningitis; surgical prophylaxis; prophylaxis of meningococcal meningitis; gonorrhoea

Contraindications:

cefalosporin hypersensitivity (see section 6.2.1); porphyria; neonates with jaundice, hypoalbuminaemia, acidosis or impaired bilirubin binding

Precautions:

penicillin sensitivity (see section 6.2.1); 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

Dosage:

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; severe infections 2–4 g daily; **infant** and **CHILD** under 50 kg 20–50 mg/kg daily; 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), **neonates** 20–50 mg/kg daily (maximum 50 mg/kg daily)

Uncomplicated gonorrhoea, *by deep intramuscular injection* , **ADULT** 125 mg as a single dose

Surgical prophylaxis, *by deep intramuscular injection or by intravenous injection* (over at least 2–4 minutes), **ADULT** 1 g at induction

Colorectal surgery (with antibacterial active against anaerobes), *by deep intramuscular injection or by intravenous injection* (over at least 2–4 minutes), *or by intravenous infusion* , 2 g as a single dose

RECONSTITUTION AND ADMINISTRATION.	According to manufacturer's directions. Intramuscular doses over 1 g 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; antibiotic-associated colitis (particularly with higher doses); allergic reactions including rashes, pruritus, urticaria, serum sickness-like reactions, fever and arthralgia, and anaphylaxis; erythema multiforme, toxic epidermal necrolysis reported; transient hepatitis and cholestatic jaundice; eosinophilia and blood disorders (including thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, confusion, hypertonia and dizziness; calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated, or those who are immobilized) or in gall bladder—consider discontinuation if symptomatic; rarely prolongation of prothrombin time, pancreatitis

Imipenem with cilastatin

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

Injection (Powder for solution for intramuscular injection), imipenem (as monohydrate) 500 mg with cilastatin (as sodium salt) 500 mg

Infusion (Powder for solution for intravenous infusion), imipenem (as monohydrate) 250 mg or 500 mg with cilastatin (as sodium salt) 250 mg or 500 mg, respectively

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.

Contraindications:

hypersensitivity to beta-lactam antibiotics (see section 6.2.1)

Precautions:

renal impairment (Appendix 4); CNS disorders, such as epilepsy; pregnancy (Appendix 2); breastfeeding (Appendix 3)

Dosage:

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, diarrhoea; antibiotic-associated colitis; taste disturbances; tooth or tongue discoloration, hearing loss; blood disorders, positive Coombs' test; allergic reactions (see section 6.2.1) including rash, pruritus, urticaria, erythema multiforme (Stevens-Johnson syndrome), fever, anaphylactic reactions, rarely toxic epidermal necrolysis, 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

Other antibacterials

Chloramphenicol

Chloramphenicol is a potent broad-spectrum antibiotic. 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 occurring mainly in sub-Saharan Africa, during which the medical services are overwhelmed by the epidemic and in which the overwhelming scale of the epidemic precludes any other form of antimicrobial therapy.

Chloramphenicol

Capsules , chloramphenicol 250 mg

Oral suspension, chloramphenicol (as palmitate) 150 mg/5 ml

Injection (Powder for solution for injection), chloramphenicol (as sodium succinate) 1-g vial

Oily injection (Suspension for injection), chloramphenicol (as sodium succinate) 500 mg/ml, 2-ml ampoule

Uses:

severe life-threatening infections, particularly those caused by *Haemophilus influenzae* , and typhoid fever; also, cerebral abscess; mastoiditis; relapsing fever; gangrene; granuloma inguinale; listeriosis; severe melioidosis; plague; psitticosis; tularaemia; Whipple disease; septicaemia; empirical treatment of meningitis

Contraindications:

pregnancy (Appendix 2); porphyria

Precautions:

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

Dosage:

Infections due to susceptible organisms (not susceptible to other antimicrobials), *by mouth or by intravenous injection or 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); **infant** under 2 weeks 25 mg/kg daily in 4 divided doses, 2 weeks to 1 year 50 mg/kg daily in 4 divided doses

Epidemics of meningococcal meningitis, *by intramuscular injection* (of oily injection), **ADULT** 3 g as a single dose, repeated after 48 hours if necessary; **INFANT** 1–8 weeks 250 mg as a single dose, 2–11 months 500 mg as a single dose; **CHILD** 1–2 years 1 g as a single dose, 3–5 years 1.5 g as a single dose, 6–9 years 2 g as a single dose, 10–14 years 2.5 g as a single dose, over 15 years as for adult; dose repeated after 48 hours if necessary

RECONSTITUTION AND ADMINISTRATION.	According to manufacturer's directions. The oily injection is for intramuscular use only (see notes above)

NOTE. Plasma concentration monitoring required in neonates and preferred in those under 4 years of age and in hepatic impairment; recommended peak plasma-chloramphenicol concentration (approximately 1 hour after intravenous injection or infusion) 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, rashes, 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; also reported in infants born to mothers treated in late pregnancy

Quinolones

Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria. It is particularly active against salmonella, shigella, campylobacter, neisseria, *Bacillus anthracis* and pseudomonas. It is also active against chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin is used with doxycycline and metronidazole to treat pelvic inflammatory disease. **Nalidixic acid** is an older quinolone effective in uncomplicated urinary-tract infections and, in the treatment of shigella in areas where it remains susceptible.

Ciprofloxacin

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

Tablets , ciprofloxacin (as hydrochloride) 100 mg [not included on WHO Model List], 250 mg

Uses:

gastroenteritis—including cholera, shigellosis, travellers' diarrhoea, campylobacter and salmonella enteritis; typhoid; gonorrhoea; chancroid; 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; prophylaxis in surgery

Contraindications:

history of tendon disorders related to quinolone use

Precautions:

history of epilepsy or conditions that predispose to seizures, G6PD deficiency, myasthenia gravis (risk of exacerbation), pregnancy (Appendix 2), breastfeeding (Appendix 3), children or adolescents (see below); avoid exposure to excessive sunlight (discontinue if photosensitivity occurs); rarely, tendon damage—discontinue at first sign of pain or inflammation and rest affected limb; hepatic impairment (Appendix 5); renal failure (Appendix 4); avoid excessive alkalinity of urine and ensure adequate fluid intake as 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 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. Ciprofloxacin is used for pseudomonal infections in cystic fibrosis (for children over 5 years), and for treatment and prophylaxis of anthrax
SKILLED TASKS.	May impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:

Infections due to susceptible organisms, *by mouth* , **ADULT** 250–750 mg twice daily

Acute uncomplicated cystitis, *by mouth* , **ADULT** 100 mg twice daily for 3 days

Gonorrhoea, chancroid, shigellosis, or cholera, *by mouth* , 500 mg as a single dose

Pseudomonal lower respiratory-tract infection in cystic fibrosis, *by mouth* , **ADULT** 750 mg twice daily; **CHILD** 5–17 years (see 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), dysphagia, tremor, hyperglycaemia, headache, dizziness, sleep disorders, rash (rarely erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis), and pruritus; vasculitis, erythema nodosum, petechiae, haemorrhagic bullae; less frequently anorexia, increase in blood urea and creatinine;

drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, paraesthesia; photosensitivity, hypersensitivity reactions including fever, urticaria, angioedema, arthralgia, myalgia, and anaphylaxis; blood disorders (including eosinophilia, leukopenia, thrombocytopenia), altered prothrombin time; disturbances in vision, taste, hearing and smell, tinnitus; tenosynovitis; tachycardia, oedema, syncope, hot flushes and sweating; also isolated reports of tendon inflammation and damage (especially in the elderly and in those taking corticosteroids), haemolytic anaemia, renal failure, interstitial nephritis, and hepatic dysfunction (including hepatitis and cholestatic jaundice); if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur discontinue

Nalidixic acid

Tablets , nalidixic acid 250 mg, 500 mg

Uses:

urinary-tract infections; shigellosis

Precautions:

history of epilepsy or conditions that predispose to seizures, G6PD deficiency, myasthenia gravis (risk of exacerbation), pregnancy (Appendix 2), breastfeeding (Appendix 3); avoid exposure to excessive sunlight (discontinue if photosensitivity occurs); rarely tendon damage—discontinue at first sign of pain or inflammation and rest affected limb; porphyria; hepatic impairment (Appendix 5); renal impairment (Appendix 4); false positive urinary glucose (if tested for reducing substances); monitor blood counts, renal and liver function if treatment exceeds 2 weeks; **interactions:** Appendix 1

Dosage:

Urinary-tract infections, *by mouth* , **ADULT** 1 g every 6 hours for 7 days, reduced in chronic infections to 500 mg every 6 hours; **CHILD** over 3 months, maximum 50 mg/kg daily in divided doses, reduced in prolonged treatment to 30 mg/kg daily

Shigellosis, *by mouth* , **ADULT** 1 g every 6 hours for 5 days; **CHILD** over 3 months, 15 mg/kg every 6 hours for 5 days

Patient Advice. Take on an empty stomach, preferably one hour before a meal

Adverse effects:

nausea, vomiting, dyspepsia, abdominal pain, diarrhoea (rarely antibiotic-associated colitis), headache, dizziness, weakness, sleep disorders, rash (rarely erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis), and pruritus; less frequently anorexia, increase in blood urea and creatinine; metabolic acidosis; drowsiness, restlessness, asthenia, depression, confusion, hallucinations, convulsions, paraesthesia, raised intracranial pressure, cranial nerve palsy; photosensitivity, hypersensitivity reactions including fever, urticaria, angioedema,

arthralgia, myalgia, and anaphylaxis; blood disorders (including eosinophilia, leukopenia, thrombocytopenia); disturbances in vision, taste, hearing and smell; also isolated reports of tendon inflammation and damage (especially in the elderly and in those taking corticosteroids); haemolytic anaemia, renal failure, interstitial nephritis, and hepatic dysfunction (including hepatitis and cholestatic jaundice); if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur discontinue

Tetracyclines

Doxycycline is a tetracycline and is a broad-spectrum antibiotic 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 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.

Doxycycline

Capsules , doxycycline (as hydrochloride) 100 mg

Uses:

respiratory-tract infections, including pneumonia and chronic bronchitis; urinary-tract infections; syphilis; chlamydia, mycoplasma, and rickettsia; prostatitis; lymphogranuloma venereum; pelvic inflammatory disease (with metronidazole); Lyme disease; brucellosis (with rifampicin); leptospirosis, scrub typhus and travellers' diarrhoea; psittacosis; cholera; melioidosis; plague; anthrax; Q fever; malaria (section 6.4.3)

Contraindications:

pregnancy (Appendix 2); children (see notes above); 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

Dosage:

Infections due to susceptible organisms, *by mouth* , **ADULT** and **CHILD** over 8 years, 200 mg on first day then 100 mg daily; in severe infections, 200 mg daily

Syphilis, *by mouth* , 100 mg twice daily for 14 days; late latent syphilis 100 mg twice daily for 28 days

Uncomplicated genital chlamydia, non-gonococcal urethritis, *by mouth* , 100 mg twice daily for 7 days (14 days in pelvic inflammatory disease)

Louse and tick-borne relapsing fevers, *by mouth* , 100 mg or 200 mg as a single dose

Cholera, *by mouth,* **ADULT** 300 mg as a single dose; **CHILD** over 8 years, 100 mg as a single dose

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

Adverse effects:

gastrointestinal disturbances; anorexia, erythema (discontinue treatment); photosensitivity; hypersensitivity reactions; headache and visual disturbances; hepatotoxicity, blood disorders, pancreatitis, and antibiotic-associated colitis reported; staining of growing teeth and occasional dental hypoplasia

Macrolides

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.

Azithromycin is more active than erythromycin against some Gram-negative organisms such as *Chlamydia trachomatis* . The concentration and persistance of azithromycin is much higher in the tissue than in plasma; a single dose of azithromycin is used in the treatment of uncomplicated genital chlamydia and trachoma. Azithromycin is **not** recommended if there is a possibility of gonorrhoea because macrolide resistance emerges rapidly when it is used in this setting.

Azithromycin

Capsules , azithromycin (as dihydrate) 250 mg or 500 mg

Oral suspension , azithromycin (as dihydrate) 200 mg/5 ml

Uses:

uncomplicated genital chlamydial infections and trachoma

Contraindications:

hepatic impairment (Appendix 5)

Precautions:

renal impairment (Appendix 4); pregnancy (Appendix 2) and breastfeeding (Appendix 3); prolongation of QT interval (ventricular tachycardia reported); **interactions:** Appendix 1

Dosage:

Uncomplicated genital chlamydial infections or trachoma, *by mouth* , **ADULT** over 45 kg 1 g as a single dose; 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, constipation; dizziness, headache, drowsiness; photosensitivity; hepatitis, interstitial nephritis, acute renal failure, asthenia, paraesthesia, convulsions and mild neutropenia reported; rarely tinnitus, hepatic necrosis, hepatic failure, and taste disturbances

Erythromycin

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

Tablets , erythromycin (as stearate) 250 mg; erythromycin (as ethyl succinate) 500 mg

Gastro-resistant tablets , erythromycin 250 mg

Gastro-resistant capsules , erythromycin 250 mg

Oral suspension , erythromycin (as stearate) 125 mg/5 ml; erythromycin (as ethyl succinate) 125 mg/5 ml

Infusion (Powder for solution for infusion), erythromycin (as lactobionate) 500-mg vial

Uses:

alternative to penicillin in hypersensitive patients; pneumonia; legionnaires' disease; syphilis; chancroid; chlamydia; non-gonococcal urethritis; prostatitis; lymphogranuloma venereum; campylobacter enteritis; relapsing fever; diphtheria and whooping cough prophylaxis

Contraindications:

hypersensitivity to erythromycin or other macrolides; porphyria

Precautions:

hepatic impairment (Appendix 5) and renal impairment (Appendix 4); prolongation of the QT interval (ventricular tachycardia reported); pregnancy (not known to be harmful); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

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

Uncomplicated genital chlamydia, non-gonococcal urethritis, *by mouth* , **ADULT** 500 mg 4 times daily for 7 days

Severe infections, *by intravenous infusion* , **ADULT** and **CHILD** 50 mg/kg daily by continuous infusion *or* in divided doses every 6 hours

Patient Advice. Gastro-resistant tablets and capsules should be swallowed whole

Adverse effects:

nausea, vomiting, abdominal discomfort, diarrhoea (and antibiotic-associated colitis); urticaria, rashes, and other allergic reactions (rarely, anaphylaxis); reversible hearing loss after large doses; cholestatic jaundice, cardiac effects (including chest pain and arrhythmias), myasthenia-like syndrome, erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis

Aminoglycosides

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.

Use of gentamicin should be restricted to trained health personnel and 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.

For most infections, doses of up to 5 mg/kg daily in divided doses are used if renal function is normal; higher doses are used occasionally for serious infections. Loading and maintenance doses are based on the patient's weight and renal function (for example, using a nomogram) with adjustments based on plasma gentamicin concentration.

Gentamicin

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

Injection (Solution for injection), gentamicin (as sulfate) 10 mg/ml, 2-ml vial; 40 mg/ml, 2-ml vial

Uses:

pneumonia; cholecystitis; peritonitis; septicaemia; acute pyelonephritis; prostatitis; skin infections; pelvic inflammatory disease; endocarditis; meningitis; listeriosis; tularaemia; brucellosis; plague; surgical prophylaxis; eye (section 21.1)

Contraindications:

myasthenia gravis

Precautions:

renal impairment (Appendix 4), infants and elderly (dosage adjustment and monitor renal, auditory, and vestibular function, and serum-gentamicin concentrations); avoid prolonged use; conditions characterized by muscular weakness; significant obesity (monitor serum-gentamicin concentration closely and possibly reduce dose); see notes above; pregnancy (Appendix 2); **interactions:** Appendix 1

Dosage:

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; **CHILD** up to 2 weeks, 3 mg/kg every 12 hours; 2 weeks–12 years, 2 mg/kg every 8 hours

Streptococcal and enterococcal endocarditis (as part of combination therapy), *by intravenous injection* (over at least 3 minutes), **ADULT** 80 mg twice daily

Surgical prophylaxis, *by intravenous injection* , **ADULT** 5 mg/kg as a single dose at induction (with clindamycin)

NOTE. One hour (peak) concentrations should not exceed 5–10 mg/litre; pre-dose (trough) concentration should be less than 2 mg/litre

DILUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects:

vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesaemia on prolonged therapy; antibiotic-associated colitis; also, nausea, vomiting, rash

Metronidazole

Metronidazole has high activity against anaerobic bacteria and protozoa (see also section 6.4.1). Metronidazole by the rectal route is an effective alternative to the intravenous route when oral administration is not possible.

Metronidazole

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

Tablets , metronidazole 200 mg, 250 mg, 400 mg, and 500 mg

Oral suspension , metronidazole (as benzoate) 200 mg/5 ml

Intravenous infusion (Solution for infusion), metronidazole 5 mg/ml, 100-ml bag

Suppositories , metronidazole 0.5 g, 1 g

Uses:

anaerobic bacterial infections, including gingivitis, pelvic inflammatory disease, tetanus, peritonitis, brain abscess, necrotizing pneumonia, antibiotic-associated colitis, leg ulcers and pressure sores and surgical prophylaxis; bacterial vaginosis; tissue nematode infections (section 6.1.1.3); trichomonal vaginitis, amoebiasis, and giardiasis (section 6.4.1); *Helicobacter pylori* eradication (section 17.1)

Contraindications:

chronic alcohol dependence

Precautions:

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

Dosage:

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; 1–5 years 250 mg; 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 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* , 200–250 mg every 8 hours for 3 days; **CHILD** 1–3 years, 50 mg every 8 hours for 3 days; 3–7 years, 100 mg every 12 hours for 3 days; 7–10 years, 100 mg every 8 hours for 3 days

Acute dental infections, *by mouth* , **ADULT** 200 mg every 8 hours for 3–7 days

Antibiotic-associated colitis, *by mouth* , 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. Metronidazole tablets should be swallowed whole with water, during or after a meal; metronidazole suspension should be taken one 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, leukopenia, on prolonged or high dosage regimens

Nitrofurantoin

Nitrofurantoin is bactericidal *in vitro* to most Gram-positive and Gram-negative urinary-tract pathogens and it is used to treat acute and recurrent urinary-tract infections. It is also used prophylactically in chronic urinary-tract infections.

Nitrofurantoin

Tablets , nitrofurantoin 50 mg [not included on WHO Model List], 100 mg

Oral suspension , nitrofurantoin 25 mg/5 ml [not included on WHO Model List]

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 or 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; elderly and debilitated; vitamin B and folate deficiency; false positive urinary glucose (if testing for reducing substances); urine may be coloured yellow or brown

Dosage:

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 (dose reduced to 200 mg daily in divided doses, if severe nausea)

Prophylaxis of urinary-tract infections (see Precautions), *by mouth* , **ADULT** 50–100 mg at night; **CHILD** over 3 months, 1 mg/kg at night

Adverse effects:

dose-related gastrointestinal disorders; nausea; hypersensitivity reactions including urticaria, rash, sialadenitis, pruritus, angioedema; anaphylaxis reported; rarely, cholestatic jaundice, hepatitis, exfoliative dermatitis; erythema multiforme, pancreatitis, arthralgia; blood disorders; pulmonary reactions (pulmonary fibrosis; possible association with lupus erythematosus-like syndrome); peripheral neuropathy; benign intracranial hypertension; transient alopecia

Spectinomycin

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.

Spectinomycin

Injection (Powder for solution for injection), spectinomycin (as hydrochloride), 2-g vial

Uses:

uncomplicated and disseminated gonorrhoea (see notes above); adult and neonatal gonococcal conjunctivitis; chancroid

Precautions:

renal impairment; pregnancy and breastfeeding

Dosage:

Uncomplicated gonococcal infections and chancroid, *by deep intramuscular injection* , **ADULT** 2 g as a single dose (may be 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, dizziness, fever, urticaria; rarely, anaphylaxis; pain at injection site

Sulfonamides and trimethoprim

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 used in the prevention of rheumatic fever recurrence. **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* infections must only be undertaken with specialist supervision where there are appropriate

monitoring facilities (section 6.4.5). **Trimethoprim** is also used alone for respiratory-tract infections and, in particular, for urinary-tract infections.

Sulfadiazine

Sulfadiazine is a complementary antibacterial drug

Tablets , sulfadiazine 500 mg

Injection (Solution for injection), sulfadiazine (as sodium salt) 250 mg/ml, 4-ml ampoule

Uses:

prevention of recurrences of rheumatic fever; toxoplasmosis (section 6.4.5)

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); avoid in blood disorders (unless under specialist supervision); monitor blood counts and discontinue immediately if blood disorder develops; rashes—discontinue immediately; predisposition to folate deficiency; elderly; asthma; G6PD deficiency; pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid in infants under 6 weeks; **interactions:** Appendix 1

Dosage:

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 rashes, 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, anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, purpura—discontinue immediately; also reported, 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

Sulfamethoxazole with trimethoprim

Tablets , sulfamethoxazole 100 mg with trimethoprim 20 mg; sulfamethoxazole 400 mg with trimethoprim 80 mg

Oral suspension , sulfamethoxazole 200 mg with trimethoprim 40 mg/5 ml

Injection (Solution for dilution for infusion), sulfamethoxazole 80 mg with trimethoprim 16 mg/ml, 5-ml and 10-ml ampoules

Uses:

urinary-tract infections; respiratory-tract infections including bronchitis, pneumonia, infections in cystic fibrosis; melioidosis; listeriosis; brucellosis; granuloma inguinale; otitis media; skin infections; *Pneumocystis carinii* pneumonia (section 6.4.5)

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); avoid in blood disorders (unless under specialist supervision); monitor blood counts and discontinue immediately if blood disorder develops; rash—discontinue immediately; predisposition to folate deficiency, elderly; asthma; G6PD deficiency; pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid in infants under 6 weeks; **interactions:** Appendix 1

Dosage:

Severe infections due to susceptible organisms (not susceptible to other antibacterials), *by mouth or by intravenous infusion* , **ADULT** sulfamethoxazole 800 mg with trimethoprim 160 mg every 12 hours, increased to sulfamethoxazole 1.2 g with trimethoprim 240 mg, every 12 hours in more severe infections; *by mouth* , **CHILD** 6 weeks–5 months, sulfamethoxazole 100 mg with trimethoprim 20 mg every 12 hours; 6 months–5 years, sulfamethoxazole 200 mg with trimethoprim 40 mg every 12 hours; 6–12 years, sulfamethoxazole 400 mg with trimethoprim 80 mg every 12 hours; *by intravenous infusion* , **CHILD** sulfamethoxazole 30 mg/kg daily with trimethoprim 6 mg/kg daily in 2 divided doses

DILUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects:

nausea, vomiting, diarrhoea, headache; hypersensitivity reactions including rashes, 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, anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, purpura—discontinue immediately; also reported,

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; megaloblastic anaemia due to trimethoprim

Trimethoprim

Tablets , trimethoprim 100 mg, 200 mg

Injection (Solution for injection), trimethoprim (as lactate) 20 mg/ml, 5-ml ampoule [not included on WHO Model List]

Uses:

urinary-tract infections; bronchitis

Contraindications:

blood disorders; porphyria

Precautions:

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

Dosage:

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

rashes, pruritus; depression of haematopoiesis; gastrointestinal disturbances including nausea and vomiting; rarely exfoliative dermatitis and toxic epidermal necrolysis, photosensitivity and other allergic reactions including angioedema and anaphylaxis; aseptic meningitis

Clindamycin

Clindamycin is a bacteriostatic antibacterial with activity against Gram-positive aerobes and a wide range of anaerobes. However, its use is limited because of adverse effects. Antibiotic-associated colitis can occur with a wide range of antibacterials, but occurs most frequently with clindamycin. It may be fatal and is most common in women and the elderly; it can develop during or after treatment with clindamycin. 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

Clindamycin is a complementary drug when penicillin is not appropriate

Capsules , clindamycin (as hydrochloride) 150 mg

Injection (Solution for injection), clindamycin (as phosphate) 150 mg/ml, 2-ml ampoule

Uses:

staphylococcal bone and joint infections; peritonitis; endocarditis prophylaxis

Contraindications:

diarrhoeal states; avoid injections containing benzyl alcohol in neonates

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; elderly; females; pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid rapid intravenous administration; **interactions:** Appendix 1

Dosage:

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 by intravenous infusion only; single doses by intravenous infusion not to exceed 1.2 g; **neonates** 15–20 mg/kg daily; **CHILD** over 1 month, 15–40 mg/kg daily in 3–4 divided doses; severe infections, at least 300 mg daily, regardless of weight

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, then 150 mg 6 hours later by mouth or infusion

Patient Advice. Patients should discontinue 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, antibiotic-associated colitis; rashes, pruritus, urticaria, and rarely anaphylaxis; erythema multiforme, exfoliative and vesiculobullous dermatitis; jaundice and altered liver function tests; neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia; pain, induration, and abscess after intramuscular injection; thrombophlebitis after intravenous injection

Vancomycin

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 methicillin-resistant staphylococcal infections, brain abscess, staphylococcal meningitis and septicaemia.

Vancomycin

Vancomycin is a complementary antibacterial drug for use only when there is significant resistance to other drugs on the WHO Model List

Infusion (Powder for solution for infusion), vancomycin (as hydrochloride) 250-mg vial

Uses:

methicillin-resistant staphylococcal pneumonia; staphylococcal meningitis; endocarditis prophylaxis (with gentamicin)

Precautions:

avoid rapid infusion (risk of anaphylactoid reactions, see Adverse effects); rotate infusion sites; renal impairment (Appendix 4); elderly; history of deafness—avoid; plasma-vancomycin concentration measured after 3 or 4 doses (earlier if renal impairment), blood counts, urinalysis, and renal function tests—use only in hospital setting; monitor auditory function and plasma-vancomycin concentrations in elderly or in renal impairment; pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

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; **infant** 1–4 weeks, 15 mg/kg initially, then 10 mg/kg every 8 hours; **CHILD** over 1 month, 10 mg/kg every 6 hours

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. Plasma concentration monitoring required; 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

Adverse effects:

nephrotoxicity including renal failure and interstitial nephritis; ototoxicity (discontinue if tinnitus occurs); blood disorders; nausea, chills, fever, eosinophilia, anaphylaxis, rashes, including exfoliative dermatitis, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis, and vasculitis; phlebitis; on rapid infusion, severe hypotension (with shock, cardiac arrest), wheezing, dyspnoea, urticaria, pruritus, flushing of the upper body ('red man' syndrome), pain and muscle spasm of back and chest

Antileprosy drugs

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 to 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 paucibacillary (PB) or multibacillary (MB) leprosy. The 2 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 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 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 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. If there is nerve involvement corticosteroids, such as oral prednisolone 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 seems to become worse, 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; 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. Treatment is continued for 6 months for PB leprosy.

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. Treatment is continued for 12 months for MB leprosy.

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 WHO Model List].

Clofazimine

Capsules, clofazimine 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 and breastfeeding; may discolour soft contact lenses

Dosage:

Multibacillary leprosy (in combination with dapsone and rifampicin, see notes 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 notes above; continue treatment for 12 months

Type 2 lepra reaction (erythema nodosum leprosum; see notes above), *by mouth* , **ADULT** and **CHILD** 200–300 mg daily in 2 or 3 divided doses; 4–6 weeks treatment may be required before 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 and diarrhoea; severe mucosal and submucosal oedema, with prolonged treatment with high doses—may be severe enough to cause subacute small-bowel obstruction (see also Precautions)

Dapsone

Tablets, dapsone 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 therapy, and monitor blood counts during treatment); susceptibility to haemolysis including G6PD deficiency (including breastfeeding affected infants); pregnancy (Appendix 2); 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

Dosage:

Paucibacillary leprosy (in combination with rifampicin, see notes above), *by mouth* , **ADULT** 100 mg daily; **CHILD** under 10 years, see notes above; 10–14 years 50 mg daily; continue treatment for 6 months

Multibacillary leprosy (in combination with rifampicin and clofazimine, see notes above), **ADULT** 100 mg daily; **CHILD** under 10 years, see notes above; 10–14 years 50 mg daily; continue treatment for 12 months

Adverse effects:

haemolysis and methaemoglobinaemia; allergic dermatitis (rarely including toxic epidermal necrolysis and the Stevens-Johnson syndrome); rarely, hepatitis and agranulocytosis; 'dapsone syndrome' resembling mononucleosis—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

Tablets, rifampicin 150 mg, 300 mg

Capsules , rifampicin 150 mg, 300 mg

Uses:

paucibacillary leprosy; multibacillary leprosy; tuberculosis (section 6.2.4)

Contraindications:

hypersensitivity to rifamycins; jaundice

Precautions:

reduce dose in hepatic impairment (Appendix 5); liver function tests and blood counts required in liver disorders, alcohol dependency, elderly, and on prolonged therapy; renal impairment (if dose above 600 mg daily); pregnancy (Appendix 2); 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 Patients or their carers should be told how to recognize signs of liver disorders and

DISORDERS. advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

Dosage:

Paucibacillary leprosy (in combination with dapsone; see notes above), *by mouth* , **ADULT** 600 mg once a month; **CHILD** under 10 years, see notes above; 10–14 years 450 mg once a month; continue treatment for 6 months

Multibacillary leprosy (in combination with dapsone and clofazimine; see notes above), *by mouth* , **ADULT** 600 mg once a month under supervision; **CHILD** under 10 years, see notes above; 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; rashes, 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); also reported, oedema, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia and menstrual disturbances; urine, tears, saliva, and sputum coloured orange-red

Antituberculosis drugs

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, but the primary infection is usually asymptomatic. 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 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 which may contribute to resistance and treatment failure has led to the development of regimens with directly supervised treatment. Directly observed treatment, short-course (DOTS) therapy which lasts for 6 or 8 months, given 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 three times weekly or daily dose regimen. Therefore, there is a greater risk of treatment failure with twice weekly regimens. Fixed-dose combination tablets incorporating 2 or more drugs are also 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.

Modern short-course therapy is usually in 2 phases. The initial phase (2 months) involves the concurrent use of at least 3 drugs to reduce the bacterial population rapidly and prevent drug-resistant bacteria emerging. The second continuation phase (4–6 months) involves fewer drugs and is used to eliminate any remaining bacteria and prevent recurrence. Direct observation of therapy is considered essential to ensure compliance in the initial phase and also useful in the continuation phase 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; **thioacetazone** is used only if ethambutol cannot be used. In supervised regimens 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** , **ciprofloxacin** , **cycloserine** , **ethionamide** , **kanamycin** , **levofloxacin** , and **ofloxacin**) for the treatment of multidrug-resistant tuberculosis should be used in specialized centres adhering to WHO standards for TB control.

Worldwide, an important predisposing cause of immunosuppression leading to tuberculosis is human immunodeficiency virus (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 cost-effective. 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.

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.

Recommended 6-month treatment regimens for tuberculosis [1]

Drug	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	15 mg/kg daily	
or		
Ethambutol	15 mg/kg daily	
Isoniazid	10 mg/kg 3 times weekly	10 mg/kg 3 times weekly
Rifampicin	10 mg/kg 3 times weekly	10 mg/kg 3 times weekly
Pyrazinamide	35 mg/kg 3 times weekly	
together with		
Streptomycin	15 mg/kg 3 times weekly	
or		
Ethambutol	30 mg/kg 3 times weekly[2]	

[1] Unless otherwise indicated, doses are suitable for both adults and children

[2] Not suitable for children

Recommended 8-month treatment regimen for tuberculosis [1]

Drug Initial phase (2 months)	Continuation phase (6 months)
Isoniazid 5 mg/kg daily	5 mg/kg daily
Rifampicin 10 mg/kg daily	
Pyrazinamide 25 mg/kg daily	
together with	
Ethambutol 15 mg/kg daily[3]	15 mg/kg daily[4]
or	
Streptomycin[2] 15 mg/kg daily	

[1] Unless otherwise indicated, doses are suitable for both adults and children

[2] Streptomycin always replaces ethambutol in meningeal TB

[3] Not suitable for children under 5 years

[4] Thioacetazone (2.5 mg/kg daily) may be used (only if ethambutol cannot be given) in combination with isoniazid in the continuation phase; risk of severe toxicity, particularly in HIV-infected individuals

Treatment regimens by category of tuberculosis diagnosis

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):
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 [2] 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):
isoniazid + rifampicin + pyrazinamide + ethambutol[3] 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 multi-drug-resistant tuberculosis (MDR-TB) (smear-positive despite supervised re-treatment) [4]

specially designed standardized or individualized regimens recommended

[1] Drug intake should be directly observed in patients who are smear positive during the initial phase, and always when rifampicin is given

[2] Drug sensitivity testing recommended before prescribing Category II treatment in failure cases; patients with MDR-TB should be prescribed Category IV regimen

[3] Omit ethambutol in initial phase if disease is not complicated by cavitary disease or concomitant HIV disease, and in patients infected with fully susceptible bacilli or young children with primary tuberculosis

[4] Early culture and sensitivity testing recommended for contacts of patients with MDR-TB

Ethambutol hydrochloride

Tablets , ethambutol hydrochloride 100 mg, 400 mg

Uses:

tuberculosis, in combination with other drugs (see notes and tables above)

Contraindications:

optic neuritis; children under 5 years—unable to report symptomatic visual disturbances; severe renal impairment

Precautions:

visual disturbances—ocular examination recommended before and during treatment (see note below); reduce dose in renal impairment (Appendix 4) and monitor plasma concentration; elderly; pregnancy (not known to be harmful); 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

Dosage:

Tuberculosis (initial phase of combination therapy; see notes and tables above), *by mouth* , **ADULT** 15 mg/kg daily *or* 30 mg/kg 3 times a week; **CHILD** 15 mg/kg daily

NOTE. 'Peak' concentration (2–2.5 hours after dose) should be 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—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, thrombocytopenia

Ethambutol hydrochloride with isoniazid

Tablets , ethambutol hydrochloride 400 mg with isoniazid 150 mg

Uses:

tuberculosis, in combination with other drugs (see notes and tables above)

Contraindications:

preparation not suitable for use in children; see Ethambutol Hydrochloride and Isoniazid

Precautions:

see Ethambutol Hydrochloride and Isoniazid

Dosage:

Tuberculosis, continuation phase of 8-month regimen in place of thioacetazone with isoniazid (see notes and tables), *by mouth* , **ADULT** ethambutol hydrochloride 800 mg and isoniazid 300 mg daily

Adverse effects:

see Ethambutol Hydrochloride and Isoniazid

Isoniazid

Tablets, isoniazid 100 mg, 300 mg

Injection (Solution for injection), isoniazid 25 mg/ml, 2-ml ampoule [not included on WHO Model List]

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 risk of peripheral neuritis; epilepsy; slow acetylator status (increased risk of adverse effects); history of psychosis; pregnancy (not known to be harmful); 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

Dosage:

Tuberculosis, treatment (combination therapy; see also notes and tables), *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 (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 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, also constipation, dry mouth; hypersensitivity reactions including fever, rashes, joint pain, erythema multiforme, purpura usually during first weeks of treatment; peripheral neuropathy; blood disorders including agranulocytosis, haemolytic anaemia, aplastic anaemia; optic neuritis, toxic psychoses, and convulsions; hepatitis (especially over age of 35 years and regular users of alcohol)—withdraw treatment; also reported, systemic lupus erythematosus-like syndrome, pellagra, hyperreflexia, difficulty with micturition, hyperglycaemia and gynaecomastia

Pyrazinamide

Tablets, pyrazinamide 400 mg, 500 mg [500-mg strength not included on WHO Model List]

Uses:

tuberculosis, in combination with other drugs (see notes and tables above)

Contraindications:

severe hepatic impairment; porphyria

Precautions:

hepatic impairment (monitor hepatic function; Appendix 5); renal impairment; 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

Dosage:

Tuberculosis (initial phase of combination therapy; see notes 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, liver failure; nausea, vomiting; arthralgia; gout; sideroblastic anaemia; rash, photosensitivity

Rifampicin

Capsules , rifampicin 150 mg, 300 mg

Uses:

tuberculosis, in combination with other drugs (see notes and tables above); leprosy (section 6.2.3)

Contraindications:

hypersensitivity to rifamycins; jaundice

Precautions:

reduce dose in hepatic impairment (Appendix 5); liver function tests and blood counts required in liver disorders, alcohol dependency, elderly, and on prolonged therapy; renal impairment (if dose above 600 mg daily); pregnancy (Appendix 2); 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

Dosage:

Tuberculosis (combination therapy; see notes and tables above), *by mouth* , **ADULT** and **CHILD** 10 mg/kg daily *or* 3 times weekly (maximum dose, 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; rashes, 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 reported; urine, tears, saliva, and sputum coloured orange-red

Rifampicin with isoniazid

Tablets, rifampicin 60 mg with isoniazid 30 mg; rifampicin 150 mg with isoniazid 75 mg; rifampicin 300 mg with isoniazid 150 mg; rifampicin 60 mg with isoniazid 60 mg; rifampicin 150 mg with isoniazid 150 mg

Uses:

tuberculosis (see notes and tables above)

Contraindications:

see under Rifampicin and Isoniazid

Precautions:

combined preparation usually not suitable for use in children; see under Rifampicin and Isoniazid

Dosage:

Tuberculosis, 6-month regimen (combination therapy; see notes and tables), *by mouth* , **ADULT** 10 mg/kg (rifampicin) and 5 mg/kg (isoniazid) daily

Tuberculosis, 6-month regimen (combination therapy; see notes and tables), *by mouth* , **ADULT** 10 mg/kg (rifampicin) and 10 mg/kg (isoniazid) 3 times a week

Adverse effects:

see under Rifampicin and Isoniazid

Rifampicin with isoniazid and pyrazinamide

Tablets , rifampicin 60 mg, isoniazid 30 mg, and pyrazinamide 150 mg; rifampicin 150 mg, isoniazid 75 mg, and pyrazinamide 400 mg; rifampicin 150 mg, isoniazid 150 mg, and pyrazinamide 500 mg

Uses:

tuberculosis, in combination with other drugs (see notes and tables above)

Contraindications:

combined preparation not suitable for use in children; see Rifampicin, Isoniazid, and Pyrazinamide

Precautions:

see Rifampicin, Isoniazid, and Pyrazinamide

Dosage:

Tuberculosis, initial phase of 6-month treatment regimens (see notes 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 a week

Adverse effects:

see Rifampicin, Isoniazid, and Pyrazinamide

Rifampicin with isoniazid, pyrazinamide and ethambutol hydrochloride

Tablets , rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol hydrochloride 275 mg

Uses:

tuberculosis (see notes and tables above)

Contraindications:

combined preparation not suitable for use in children; see Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride

Precautions:

see Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride

Dosage:

Tuberculosis, induction phase of 6-month regimen (see notes and tables above), *by mouth* , **ADULT** rifampicin 10 mg/kg, isoniazid 5 mg/kg, pyrazinamide 25 mg/kg, and ethambutol hydrochloride 15 mg/kg daily

Adverse effects:

see Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride

Streptomycin

Injection (Powder for solution for injection), streptomycin (as sulfate) 1-g vial

Uses:

tuberculosis, in combination with other drugs (see notes and tables above)

Contraindications:

hearing disorders; myasthenia gravis; pregnancy (Appendix 2)

Precautions:

children—painful injection, avoid use if possible; renal impairment (Appendix 4), infants, and elderly (dosage adjustment and monitor renal, auditory, and vestibular function, and plasma streptomycin concentrations); **interactions:** Appendix 1

Dosage:

Tuberculosis (initial phase of combination therapy; see notes and tables above), *by deep intramuscular injection* , **ADULT** and **CHILD** 15 mg/kg daily *or* 3 times a week (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) 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, rash; rarely, haemolytic anaemia, aplastic anaemia, agranulocytosis, thrombocytopenia; pain and abscess at injection site

Thioacetazone with isoniazid

Thioacetazone with isoniazid is a complementary drug combination

Tablets , thioacetazone 50 mg with isoniazid 100 mg; thioacetazone 150 mg with isoniazid 300 mg

Uses:

tuberculosis, in combination with other drugs (see notes and tables above)

Contraindications:

see Isoniazid; hepatic impairment; renal impairment; HIV infection—thioacetazone associated with high incidence of serious, sometimes fatal cutaneous hypersensitivity reactions, including exfoliative dermatitis

Precautions:

see Isoniazid; determine efficacy and toxicity of thioacetazone—geographical differences; hypersensitivity reactions—withdraw treatment; **interactions:** Appendix 1

Dosage:

Tuberculosis, continuation phase of 8-month regimen (see notes and tables above), *by mouth* , **ADULT** and **CHILD** thioacetazone 2.5 mg/kg daily and isoniazid 5 mg/kg daily

Adverse effects:

see Isoniazid; thioacetazone causes the following—nausea, vomiting, diarrhoea; hypersensitivity reactions including conjunctivitis, vertigo, rashes; fatal exfoliative dermatitis, acute hepatic failure reported; also, agranulocytosis, thrombocytopenia and aplastic anaemia

BCG vaccine

BCG vaccine should comply with the recommendations published in the report of the WHO Expert Committee on Biological Standardization, WHO Technical Report Series, No. 745, 1987 and Amendment 1987, WHO Technical Report Series, No. 771, 1988

Injection (Powder for solution for injection), live bacteria of a strain derived from the bacillus of Calmette and Guérin

Uses:

for active immunization against tuberculosis; see also section 19.3.1.1

Contraindications:

see section 19.3.1; generalized oedema; hypogammaglobulinaemia and immunodeficiency due to antimetabolites, irradiation, corticosteroids; HIV positive—except asymptomatic children in areas of high tuberculosis risk; malignant disease; antimycobacterial treatment

Precautions:

see section 19.3.1; pregnancy (Appendix 2); eczema, scabies—vaccine site must be lesion-free; **interactions:** Appendix 1

Dosage:

NOTE. National immunization schedules may vary

Immunization against tuberculosis, *by intradermal injection* , **infants** up to 3 months, 0.05 ml; **ADULT** and **CHILD** over 3 months 0.1 ml

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects:

lymphadenitis and keloid formation; osteitis and localized necrotic ulceration; rarely, disseminated BCG infection in immunodeficient patients; rarely, anaphylaxis

Tuberculin purified protein derivative (tuberculin PPD)

All tuberculins should comply with the WHO Requirements for Tuberculins (revised 1985). WHO Expert Committee on Biological Standardization Thirty-sixth report (WHO Technical Report Series, No. 745, 1987, Annexe 1)

Injection , tuberculin purified protein derivative 10 units/ml, 100 units/ml

Uses:

test for hypersensitivity to tuberculoprotein

Contraindications:

should not be used within 3 weeks of receiving a live viral vaccine

Precautions:

elderly; malnutrition, viral or bacterial infections (including HIV and severe tuberculosis), malignant disease, corticosteroid or immunosuppressant therapy—diminished sensitivity to tuberculin; avoid contact with open cuts, abraded or diseased skin, eyes or mouth

Dosage:

NOTE. National recommendations may vary

Test for hypersensitivity to tuberculoprotein, *by intradermal injection* , **ADULT** and **CHILD** 5 or 10 units (1 unit may be used 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

Antifungal drugs

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 active against algal *Prototheca* spp. and against the *Leishmania protozoa* . It is used for the empirical treatment of serious fungal infections and is used 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 is liable to cause nephrotoxicity. Duration of therapy varies with 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. Intrathecal infusion has been used successfully in patients with meningeal coccidioidomycosis.

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 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, 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* . 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, footware 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 prophylaxis and treatment of candidosis.

Potassium iodide aqueous oral solution is a clear liquid with a characteristic, strong salty taste. It is effective against sporotrichosis and subcutaneous phycomycosis, which are fungal infections caused by *Sporothrix schenckii* and *Basidiobolus haptosporus* respectively. In subcutaneous sporotrichosis, amphotericin B is often effective in patients unable to tolerate iodides. Itraconazole, by mouth has been tried as an alternative to potassium iodide in both cutaneous and extracutaneous sporotrichosis. In phycomycosis, fluconazole may be effective.

Amphotericin B

Amphotericin B is a complementary antifungal drug

Injection (Powder for solution for injection), amphotericin B 50-mg vial

Uses:

life-threatening fungal infections including histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, aspergillosis, cryptococcosis, mucormycosis, sporotrichosis, and candidosis; leishmaniasis (section 6.4.2)

Precautions:

close medical supervision throughout treatment and initial test dose required (see note, below); renal impairment (Appendix 4); hepatic and renal function tests; blood counts and plasma electrolyte monitoring; corticosteroids (avoid, except to control reactions); pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid rapid infusion (risk of arrhythmias); **interactions:** Appendix 1

ANAPHYLAXIS. Anaphylaxis occurs rarely with intravenous amphotericin B and a test dose is

advisable before the first infusion. The patient should be observed for about 30 minutes after the test dose

Dosage:

Systemic fungal infections, *by intravenous infusion* , **ADULT** and **CHILD** initial test dose of 1 mg over 20–30 minutes, then 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 usually necessary; if interrupted for longer than 7 days, recommence at 250 micrograms/kg daily and increase 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, and 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 above); pain and thrombophlebitis at injection site

Fluconazole

Fluconazole is a representative azole antifungal. Various drugs can serve as alternatives

Capsules , fluconazole 50 mg

Oral suspension (Powder for oral suspension), fluconazole 50 mg/5 ml

Infusion (Solution for infusion), fluconazole 2 mg/ml, 25-ml bottle, 100-ml bottle

Uses:

systemic mycoses including histoplasmosis, non-meningeal coccidioidomycosis, paracoccidioidomycosis and blastomycosis; treatment and, in AIDS and other immunosuppressed patients, prophylaxis of cryptococcal meningitis; oesophageal and oropharyngeal candidosis, vaginal candidosis and systemic candidosis

Precautions:

renal impairment (Appendix 4); pregnancy (Appendix 2); breastfeeding (Appendix 3); monitor liver function—discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis; Appendix 5); **interactions:** Appendix 1

Dosage:

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, then 400 mg daily for 8 weeks; **CHILD** 6–12 mg/kg daily (every 72 hours in **neonates** up to 2 weeks old, every 48 hours in **neonates** 2–4 weeks old)

Prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy, *by mouth 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 initial dose, then 200 mg daily for at least 4 weeks; **CHILD** 6–12 mg/kg daily (every 72 hours in **neonates** up to 2 weeks old, and every 48 hours in **neonates** 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, then 3 mg/kg daily (every 72 hours in **neonates** up to 2 weeks old, every 48 hours in **neonates** 2–4 weeks old)

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

Adverse effects:

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

Flucytosine

Flucytosine is a complementary drug

Capsules , flucytosine 250 mg

Infusion (Solution for infusion), flucytosine 10 mg/ml, 250-ml infusion

Uses:

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

Precautions:

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

Dosage:

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

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 starting next infusion (or before next dose by mouth); plasma concentration for optimum response 25–50 mg/litre—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, vertigo; blood disorders including leukopenia, potentially fatal thrombocytopenia and aplastic anaemia

Griseofulvin

Tablets , griseofulvin 125 mg, 250 mg

Capsules, griseofulvin 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 and related disorders

Precautions:

pre-existing hepatic insufficiency (closely monitor hepatic function throughout treatment); blood disorders (monitor blood count weekly during first month of treatment); breastfeeding; **interactions:** Appendix 1

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

Dosage:

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 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; 6 months for fingernails and 12 months or more for toenails

Adverse effects:

headache, nausea, vomiting, diarrhoea, rashes, dizziness, fatigue reported; dry mouth and angular stomatitis; leukopenia, agranulocytosis; proteinuria reported; photosensitivity; lupus erythematosus, toxic epidermal necrolysis, erythema multiforme; serum sickness, angioedema; peripheral neuropathy; confusion and impaired coordination

Nystatin

Tablets , nystatin 100 000 units, 500 000 units

Oral suspension, nystatin 100 000 units/ml [not included on WHO Model List]

Lozenge , nystatin 100 000 units

Pessaries , nystatin 100 000 units

Uses:

oral, oesophageal, intestinal, vaginal, and cutaneous candidosis

Precautions:

pregnancy and breastfeeding (Appendices 2 and 3)

Dosage:

Oral candidosis, *by mouth* , **ADULT** and **CHILD** over 1 month, 100 000 units after food 4 times daily

Intestinal and oesophageal candidosis, *by mouth* , **ADULT** 500 000 units 4 times daily; **CHILD** over 1 month 100 000 units 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, diarrhoea at high doses; oral irritation and sensitization; rash and rarely, erythema multiforme (Stevens-Johnson syndrome)

Potassium iodide

Potassium iodide is a complementary drug

Oral solution , potassium iodide 1 g/ml (saturated solution)

Uses:

sporotrichosis; subcutaneous phycomycosis; thyrotoxicosis (section 18.8)

Contraindications:

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

Precautions:

Addison disease; cardiac disease; hyperthyroidism; myotonia congenita; renal impairment

Dosage:

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 lower dosage

Adverse effects:

goitre, hypothyroidism, hyperthyroidism; iodism characterized by metallic taste, increased salivation, coryza and irritation and swelling of the eyes (resulting from prolonged administration); also gastrointestinal disturbances and diarrhoea; pulmonary oedema, bronchitis; depression, insomnia, impotence, headache reported

Antiprotozoal drugs

Antiamoebic, antigiardial and antitrichomonal drugs

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 furoate** is most widely used, but other compounds, including **clefamide** , **etofamide** , and **teclozan** , are also effective. Treatment with diloxanide furoate is regarded as successful if stools are free of *E. histolytica* for one month. Several specimens should be examined in evaluating response to treatment.

Symptomatic (invasive) amoebiasis may be classified as intestinal or extra-intestinal. Intestinal amoebiasis is either amoebic dysentery or non-dysenteric amoebic colitis.

Extra-intestinal amoebiasis most commonly involves the liver, but may involve the skin, genito-urinary tract, lung and brain. Invasive amoebiasis is more likely in malnutrition, immunosuppression and pregnancy. Amoebic dysentery may take a fulminating course in late pregnancy and the puerperium; 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** and **tinidazole** followed by a luminal amoebicide 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 genito-urinary tract caused by *Trichomonas vaginalis* and transmission is usually sexual. In women it causes vaginitis although some are asymptomatic. It is usually asymptomatic in men but may cause urethritis. Patients and their sexual partners should be treated with **metronidazole** or other nitroimidazole.

Diloxanide furoate

Tablets, diloxanide furoate 500 mg

Uses:

amoebiasis (asymptomatic carriers in non-endemic areas; eradication of residual luminal amoebae after treatment of invasive disease with other drugs)

Precautions:

pregnancy (defer treatment until after first trimester, Appendix 2); breastfeeding (Appendix 3)

Dosage:

Amoebiasis (see 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

Metronidazole is a representative antibacterial and antiprotozoal agent. Various drugs can serve as alternatives

Tablets , metronidazole 200 mg, 250 mg, 400 mg, 500 mg

Oral suspension, metronidazole (as benzoate) 200 mg/5 ml

Intravenous infusion (Solution for infusion), metronidazole 5 mg/ml, 100-ml bag

Uses:

invasive amoebiasis and giardiasis; trichomoniasis; tissue nematode infections (section 6.1.1.3); bacterial infections (section 6.2.2.6); *Helicobacter pylori* eradication (section 17.1)

Contraindications:

chronic alcohol dependence

Precautions:

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

Dosage:

Invasive amoebiasis, *by mouth* , **ADULT** and **CHILD** 30 mg/kg daily in 3 divided doses for 8–10 days; subsequent course of luminal amoebicide (see notes 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 notes 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; metronidazole suspension should be taken one 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, leukopenia, on prolonged or high dosage regimens

Antileishmanial drugs

Leishmaniasis is caused by the parasitic protozoa *Leishmania* . It can be categorized as visceral, cutaneous or mucocutaneous. It may be a self-limiting localized skin lesion but may range from this to disseminated progressive disease. In endemic areas there is usually a reservoir of disease in a mammalian host and the usual vectors are sandflies.

VISCERAL LEISHMANIASIS

Visceral leishmaniasis (kala-azar) is caused by *Leishmania donovani* and *L. infantum* (Old World) and by *L. chagasi* (New World), and it is usually responsive initially to the **pentavalent antimony compounds** , **meglumine antimoniate** or **sodium stibogluconate** . Both dosage and duration of treatment need to be adjusted according to the clinical response. Patients are considered to be clinically cured when no parasites are detected in splenic or bone marrow aspirates. However, biopsies should be repeated after 3 and 12 months since relapse is frequent. Antimonials combined with **allopurinol** , **pentamidine isetionate** and **amphotericin B** have been used with success in patients in relapse who have become unresponsive to antimonials alone.

CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis comprises two conditions. The Old World variety is caused by *L. tropica* , *L. major* , *L. infantum* and *L. aethiopica* . The New World variety is caused by *L. amazonensis* , *L. mexicana* , *L. peruviana* , *L. guyanensis* , *L. panamensis* and *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* and *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 or when

obstruction of lymphatic drainage or destruction of cartilage creates a risk of serious disfigurement or disability, antimonials should be administered systemically as well as locally. Infections due to *L. braziliensis* and the less common *L. panamensis* should be treated with antimonials because of the risk of mucosal involvement. *L. aethiopica* is less responsive at conventional doses 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* and *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, more extended courses of treatment are often successful. Patients who still fail to respond should receive **amphotericin B** or **pentamidine isetionate** , 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, and 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 isetionate** may be needed until clinical immunity is established.

Pentavalent antimony compounds

Meglumine antimoniate is a representative pentavalent antimony compound used to treat leishmaniasis; sodium stibogluconate can serve as an alternative

Injection (Solution for injection), pentavalent antimony (as meglumine antimoniate) 85 mg/ml, 5-ml ampoule; pentavalent antimony (as sodium stibogluconate) 100 mg/ml, 100-ml bottle

Uses:

leishmaniasis (see notes above)

Contraindications:

severe kidney disorders; breastfeeding

Precautions:

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—reduce dose or withdraw treatment if abnormalities occur; pregnancy—in potentially fatal visceral leishmaniasis, treat without delay; intravenous injections must be given slowly over 5 minutes (to reduce risk of local thrombosis) and stopped if coughing or substernal pain; mucocutaneous disease (see below); treat intercurrent infection (for example pneumonia)

MUCOCUTANEOUS DISEASE. Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around lesions (may be life-threatening if pharyngeal or tracheal involvement)—may require corticosteroids

Dosage:

NOTE. Doses are expressed in terms of pentavalent antimony

Visceral leishmaniasis, *by intramuscular injection* , **ADULT** and **CHILD** 20 mg/kg daily for a minimum of 20 days; if relapse, retreat immediately with same daily dosage

Cutaneous leishmaniasis (except *L. aethiopica* , *L. braziliensis* , *L. amazonensis*), *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; *by intramuscular injection* , **ADULT** and **CHILD** 10–20 mg/kg daily until a few days after clinical cure and negative slit-skin smear; relapse is unusual

Cutaneous leishmaniasis (*L. braziliensis*), *by intramuscular injection* , **ADULT** and **CHILD** 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 (*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 (*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. Sodium stibogluconate may be given by intramuscular injection or by slow intravenous injection (over at least 5 minutes). Both may be administered intralesionally

Adverse effects:

anorexia, nausea, vomiting, abdominal pain, ECG changes (possibly requiring dose reduction or withdrawal), headache, lethargy, myalgia; raised liver enzymes; renal function impairment; coughing and substernal pain (see Precautions); rarely

anaphylaxis, fever, sweating, flushing, vertigo, bleeding from nose or gum, jaundice, rash; pain and thrombosis on intravenous administration; pain on intramuscular injection

Pentamidine isetionate

Pentamidine isetionate is a complementary antiprotozoal and antipneumocystis drug

Injection (Powder for solution for injection), pentamidine isetionate 200-mg vial, 300-mg vial

Uses:

leishmaniasis (see notes, above); African trypanosomiasis (section 6.4.4.1); *Pneumocystis carinii* pneumonia (section 6.4.5)

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; leukopenia, thrombocytopenia, anaemia; immunodeficiency—if acute deterioration in bone marrow, renal or pancreatic function, interrupt or discontinue treatment; renal impairment (Appendix 4); pregnancy—in potentially fatal visceral leishmaniasis, treat without delay (Appendix 2); breastfeeding (Appendix 3); carry out laboratory monitoring according to manufacturer's literature

Dosage:

Visceral leishmaniasis (unresponsive to or intolerant of pentavalent antimony 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 two consecutive splenic aspirates taken 14 days apart are negative

Cutaneous leishmaniasis (*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 (*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 leishmanisais (*L. braziliensis* , *L. aethiopica*), *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 no longer visible

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions. Deep intramuscular injection is the preferred route of administration. Pentamidine isetionate is toxic; care required 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, Stevens-Johnson syndrome, reported; pain, local induration, sterile abscess and muscle necrosis at injection site

Amphotericin B

Amphotericin B is a complementary drug for the treatment of leishmaniasis

Injection (Powder for solution for injection), amphotericin B 50-mg vial

Uses:

visceral and mucocutaneous leishmaniasis unresponsive to pentavalent antimony compounds; fungal infections (section 6.3)

Precautions:

close medical supervision throughout treatment and initial test dose required (see note below); renal impairment (Appendix 4); hepatic and renal function tests; blood counts and plasma electrolyte monitoring; corticosteroids (avoid except to control reactions); pregnancy (Appendix 2); breastfeeding (Appendix 3); avoid rapid infusion (risk of arrhythmias); **interactions:** Appendix 1

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

Dosage:

Visceral and mucocutaneous leishmaniasis (unresponsive to pentavalent antimony compounds), *by intravenous infusion* , **ADULT** initial test dose of 1 mg over 20–30 minutes, then, 5–10 mg, increased by 5–10 mg daily up to maximum of 0.5–1 mg/kg, which is then administered on alternate days (total cumulative dose of 1–3 g 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, and 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 above); pain and thrombophlebitis at injection site

Antimalarial drugs

Human malaria, which is transmitted by anopheline mosquitoes (and rarely by congenital transmission, transfusion of infected blood or use of contaminated syringes among drug addicts), is caused by four species of plasmodial parasites. *Plasmodium vivax* is the most extensively distributed and causes much debilitating disease. *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 the relapses characteristic of malaria. 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.

Treatment of malaria

Blood schizontocides, which suppress malaria by destroying the asexual blood forms of the parasites, are the mainstay of the treatment of acute malaria and some are used for prophylaxis. 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 by *P. vivax* and *P. ovale* .

Some antimetabolites act synergistically when given in combination. For example, **pyrimethamine** in combination with a sulfonamide (**sulfadoxine**) or sulfone and some antibiotics (for example **doxycycline**) are blood schizontocides. Because they act more slowly, these substances are of little value when used alone. The tetracyclines are used primarily as adjuncts to quinine where multiple-drug-resistant *P. falciparum* is prevalent.

Chloroquine , a rapidly acting schizontocide, is well tolerated, safe and inexpensive. It should be used to treat malaria wherever the parasites remain susceptible. *P. malariae* and *P. ovale* remain fully sensitive to chloroquine. However, chloroquine-resistant strains of *P. falciparum* are widespread in south-east Asia, parts of the Indian subcontinent, South America, Africa and Oceania; strains of *P. vivax* in Papua New Guinea and Indonesia are also resistant to chloroquine.

A 3-day course of chloroquine by mouth is sufficient to eliminate susceptible *P. falciparum* infections because effective plasma-chloroquine concentration is sustained for several weeks.

If subsequent relapse occurs in *P. ovale* and *P. vivax* infections **primaquine** should be administered, after a second course of chloroquine, to eliminate the intrahepatic infection.

Amodiaquine is an alternative to chloroquine for the treatment of uncomplicated *P. falciparum* infection; but cross-resistance with chloroquine exists in some areas. It should preferably be used as part of combination therapy with other antimalarials, for example artesunate. Hepatitis and blood disorders were reported when amodiaquine was used for prophylaxis of malaria; patients should be told how to recognise the symptoms of these conditions and advised to seek medical help if they occur.

The combination of **sulfadoxine with pyrimethamine** is recommended for the treatment of malaria only in areas of high chloroquine resistance. A single dose of sulfadoxine with pyrimethamine is usually sufficient to eliminate infection; quinine should also be given for 3 days in patients in whom quinine may accelerate reduction of parasitaemia and in those at risk of fulminating disease. However, resistance to these combinations is now widespread, particularly in south-east Asia and South America and it occurs at low prevalence in east and central Africa. Because sulfonamides are associated with a risk of haemolysis and methaemoglobinaemia in the newborn, quinine is preferred to treat chloroquine-resistant malaria during pregnancy (see note on quinine).

Mefloquine remains effective except in certain areas of resistance in Thailand, Myanmar and Cambodia. No parenteral preparations are currently available, and it is thus suitable only for patients who can take drugs by mouth. It is generally well tolerated, although, some adverse effects have been reported (see notes). However, because of the danger of the emergence of mefloquine-resistant strains of *P. falciparum* and because of its potential toxicity, it should be used only following either microscopic or careful clinical diagnosis of *P. falciparum* infections that are known or strongly suspected to be resistant to chloroquine or sulfadoxine with pyrimethamine.

Quinine , given orally, should be reserved for *P. falciparum* infections 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 schizontocide, should be given in combination with quinine except in pregnant women and children under 8 years.

In multi-drug resistant malaria, preparations of **artemisinin** or its derivatives (**artemether** or **artesunate**) offer the only prospect of cure. They should not be used in the first trimester of pregnancy. For the treatment of multiresistant falciparum malaria oral **artesunate** may be an effective antimalarial. It should always be given in combination with mefloquine. Parenteral artemether or artesunate, whose use is restricted, are effective alternatives to quinine for the treatment of severe falciparum malaria and are preferred in areas where decreased efficacy of quinine has been documented. To ensure radical cure following parenteral treatment with artemether or

oral treatment with artesunate, a full therapeutic dose of mefloquine should be given. A fixed-dose oral formulation of **artemether with lumefantrine** has recently become available and is recommended for the treatment of uncomplicated falciparum malaria in areas with significant resistance. The combination is not for use in pregnancy or breastfeeding.

Prophylaxis against malaria

No drug regimen gives assured protection to everybody, and indiscriminate use of antimalarials can increase the risk of inducing resistance.

Chloroquine , which is usually well tolerated at the required dosage, is preferred where *P. falciparum* remains fully sensitive. The combination of proguanil with chloroquine may overcome mild chloroquine resistance. Chloroquine must be started 1 week before exposure, and be continued in pregnant women until after delivery and for at least 4 weeks after the last risk of exposure in the case of 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.

Mefloquine may be used for prophylaxis in areas of high risk or where multiple-drug 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 may 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.

Proguanil , a predominantly tissue schizontocide with little blood schizontocidal activity, is a causal prophylactic agent since it is active against pre-erythrocytic intrahepatic forms, particularly of *P. falciparum* . The latent persistent liver forms of *P. ovale* and *P. vivax* are unresponsive. However, there is evidence that it may be effective against *P. vivax* only immediately after the initial infection. *P. falciparum* resistance to proguanil or related compounds may occur in malaria endemic areas and particularly where it has been employed in mass prophylaxis. Proguanil is used for prophylaxis with chloroquine in areas where there is resistance to chloroquine but a low risk of infection as it may give some protection against *P. falciparum* and may alleviate symptoms if an attack occurs. Proguanil and chloroquine may also be used prophylactically in areas of high risk or multi-drug resistance as a second choice where mefloquine is not appropriate.

There is no evidence that proguanil is harmful in prophylactic doses during pregnancy. Because of the vulnerablility 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 or with chloroquine, if the latter alone is unlikely to be effective.

Amodiaquine

Amodiaquine is a restricted drug used for the treatment of malaria

Tablets , amodiaquine base (as hydrochloride) 153 mg, 200 mg

Uses:

treatment of uncomplicated malaria caused by *P. falciparum*

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

Dosage:

NOTE. All doses are in terms of the base

Treatment of uncomplicated falciparum malaria, *by mouth* **ADULT** and **CHILD** over 20 kg, initially 7.5 mg/kg twice daily for 1 day then 5 mg/kg twice daily for 2 days; total dose, 35 mg/kg over 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, neuromyopathy

Artemether

Artemether is a complementary antimalarial drug for restricted use in the treatment of malaria

Oily injection (Solution for injection) artemether 80 mg/ml, 1-ml ampoule

Uses:

treatment of severe *P. falciparum* malaria in areas where evidence that quinine is ineffective

Contraindications:

first trimester of pregnancy

Precautions:

SKILLED TASKS. Dizziness may impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:

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 to maximum of 7 days; this is followed by a single dose of mefloquine 15 mg/kg (or occasionally, if necessary 25 mg/kg) 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 with lumefantrine

Tablets , artemether 20 mg with lumefantrine 120 mg

Uses:

treatment of acute uncomplicated malaria due to *Plasmodium falciparum* or mixed infections including *P. falciparum* in areas with significant drug resistance

Contraindications:

pregnancy (Appendix 2); breastfeeding (Appendix 3); history of arrhythmias, of clinically relevant bradycardia, and of congestive heart failure accompanied by reduced left ventricular ejection fraction; family history of sudden death or of congenital prolongation of QTc interval (also see Precautions)

Precautions:

electrolyte disturbances, concomitant administration of drugs that prolong QT interval; monitor patients unable to take food (greater risk of recrudescence); severe renal impairment (Appendix 4) or hepatic impairment (Appendix 5); **interactions:** Appendix 1

SKILLED TASKS. Dizziness may impair ability to perform skilled tasks, for example operating machinery, driving

Dosage:

Treatment of uncomplicated falciparum malaria, *by mouth* , **ADULT** and **CHILD** over 12 years and 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 10–14 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; palpitations; arthralgia, myalgia; cough; asthenia, fatigue; pruritus, rash

Artesunate

Artesunate is a complementary antimalarial drug for restricted use in the treatment of malaria

Tablets , artesunate 50 mg

Uses:

treatment of uncomplicated *P. falciparum* malaria in areas of multiple-drug resistance

Contraindications:

first trimester of pregnancy

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, driving

Dosage:

Treatment of uncomplicated malaria (in areas of multiple-drug resistance), *by mouth* , **ADULT** and **CHILD** over 6 months, 4 mg/kg daily for 3 days; a single dose of mefloquine 15 mg/kg (or occasionally 25 mg/kg, if necessary) is given on day 2 or 3 to effect a radical cure; if artesunate used alone, 4 mg/kg on day 1, then 2 mg/kg daily for 6 days

Adverse effects:

headache, nausea, vomiting, abdominal pain, diarrhoea, dizziness, tinnitus, neutropenia, elevated liver enzyme values; ECG abnormalities, including prolongation of QT interval; temporary suppression of reticulocyte response and induction of blackwater fever, reported; neurotoxicity—in *animal* studies

Chloroquine

Tablets , chloroquine base (as phosphate or sulfate) 100 mg, 150 mg

Oral syrup , chloroquine base (as phosphate or sulfate) 50 mg/5 ml

Injection (Solution for injection), chloroquine base (as phosphate or sulfate) 40 mg/ml, 5-ml ampoule

Uses:

treatment of acute malaria caused by *P. malariae* and susceptible *P. falciparum* ; *P. vivax* and *P. ovale* (followed by primaquine to eliminate intrahepatic forms); prophylaxis of malaria for pregnant women and non-immune individuals at risk; rheumatic disorders (section 2.4)

Precautions:

if patient continues to deteriorate after chloroquine—suspect resistance and administer quinine intravenously as emergency measure; hepatic impairment; renal impairment (Appendix 4); pregnancy (but in malaria, benefit considered to outweigh risk; Appendix 2); breastfeeding (Appendix 3); may exacerbate psoriasis; neurological disorders (avoid for prophylaxis if history of epilepsy); may aggravate myasthenia gravis; severe gastrointestinal disorders; G6PD deficiency; avoid concurrent therapy with hepatotoxic drugs; **interactions:** Appendix 1

Dosage:

NOTE. All doses are in terms of the base

Treatment of 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 immediately readministered

Treatment of malaria (in patients unable to take chloroquine by mouth, but quinine preferred in falciparum malaria), *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* (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.	Warn travellers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return
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; rashes; pruritus—may become intolerable; bone-marrow suppression; hypersensitivity reactions such as urticaria and angioedema; atrioventricular block (may be result of inappropriate self-medication); porphyria and psoriasis in susceptible individuals

Doxycycline

Doxycycline is a complementary drug for the treatment of malaria

Capsules , doxycycline (as hydrochloride) 100 mg

Dispersible tablets , doxycycline (as monohydrate) 100 mg

Uses:

supplement to quinine in treatment of multiple-drug resistant *P. falciparum* malaria (where quinine resistance, in cases of hypersensitivity to sulfonamides); short-term prophylaxis of multiple-drug resistant *P. falciparum* malaria; bacterial infections (section 6.2.2.3)

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

Dosage:

Supplement to malaria treatment (see notes 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; erythema (discontinue treatment); photosensitivity; hypersensitivity reactions; headache and visual disturbances; hepatotoxicity, blood disorders, pancreatitis and antibiotic-associated colitis reported; staining of growing teeth and occasional dental hypoplasia

Mefloquine

Mefloquine is a complementary drug for the treatment of malaria

Tablets , mefloquine (as hydrochloride) 250 mg

Uses:

treatment of uncomplicated malaria due to multiple-resistant *P. falciparum* ; treatment of severe and complicated malaria, after quinine; adjunct to treatment with artemisinin and derivatives; prophylaxis of malaria for travellers to areas where high risk of multiple-resistant *P. falciparum*

Contraindications:

history of neuropsychiatric disorders including depression or convulsions; hypersensitivity to quinine

Precautions:

pregnancy (use only if other antimalarials 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 adverse effects associated with mefloquine and if they occur advised to seek medical advice on alternative antimalarials

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; effects may persist for up to 3 weeks

Dosage:

NOTE. All doses are in terms of the base

Treatment of malaria, *by mouth* , **ADULT** and **CHILD** 15 mg/kg (up to maximum of 1 g) as a single dose (increased to 25 mg/kg in areas of resistance)

Prophylaxis of malaria, *by mouth* , **ADULT** 250 mg once a week; **CHILD** over 15 kg, 5 mg/kg once a week; prophylaxis should start 1–3 weeks before departure and continue for 4 weeks after last exposure, see notes above

PATIENT ADVICE. Warn travellers about the importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of potential exposure

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, vestibular disorders; convulsions, anxiety, depression, 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

Tablets , primaquine (as phosphate) 7.5 mg, 15 mg

Uses:

elimination of intrahepatic forms of *P. vivax* and *P. ovale* (after standard chloroquine therapy); elimination of gametocytes of *P. falciparum* (after routine therapy with a blood schizontocide)

Contraindications:

pregnancy (treatment with primaquine should be delayed until after delivery; Appendix 2); breastfeeding (Appendix 3); conditions that predispose to granulocytopenia (including active rheumatoid arthritis and lupus erythematosus)

Precautions:

monitor blood count; if methaemoglobinaemia or haemolysis occurs, withdraw treatment and consult physician; G6PD deficiency (exclude before radical treatment for *P. vivax* and *P. ovale* , but not before single dose gametocytocidal treatment)

Dosage:

NOTE. All doses are in terms of the 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* (after routine blood schizontocide therapy), *by mouth* , **ADULT** and **CHILD** 500–750 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

Proguanil hydrochloride

Tablets , proguanil hydrochloride 100 mg

Uses:

with chloroquine, prophylaxis of malaria in areas of low resistance

Contraindications:

use in areas of known resistance to either proguanil or pyrimethamine

Precautions:

renal impairment (Appendix 4); pregnancy (folate supplements required, Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

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. Warn travellers about the importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return

Adverse effects:

mild gastric intolerance, diarrhoea; occasional mouth ulcers and stomatitis; skin reactions and hair loss reported; rarely hypersensitivity reactions such as urticaria and angioedema

Quinine

Tablets , quinine sulfate 300 mg; quinine bisulfate 300 mg

Injection (Solution for dilution for infusion), quinine dihydrochloride 300 mg/ml, 2-ml ampoule

Uses:

multiple-drug resistant *P. falciparum* malaria

Contraindications:

haemoglobinuria; optic neuritis; tinnitus

Precautions:

atrial fibrillation, conduction defects, heart block; monitor for signs of cardiac toxicity and blood glucose levels (with intravenous use); pregnancy (but appropriate for treatment of malaria, Appendix 2); renal impairment (Appendix 4); G6PD deficiency; may aggravate myasthenia gravis; **interactions:** Appendix 1

Dosage:

NOTE. Quinine (anhydrous base) 100 mg = quinine bisulfate 169 mg = quinine dihydrochloride 122 mg = quinine sulfate 121 mg

Quinine bisulfate 300 mg tablets provide *less* quinine than 300 mg of the sulfate or dihydrochloride

Treatment of multiple-drug 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 also used

Patient advice. If all or part of a dose is vomited within one hour, the same amount must be readministered immediately

Treatment of multiple-drug resistant *P. falciparum* malaria (in patients unable to take quinine by mouth), *by slow intravenous infusion* (over 4 hours), **ADULT** 20 mg/kg (quinine dihydrochloride) followed by 10 mg/kg (quinine dihydrochloride) every 8 hours; **CHILD** 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, rashes, 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 CNS effects; very toxic in overdosage—immediate medical attention required

Sulfadoxine with pyrimethamine

Sulfadoxine with pyrimethamine are complementary drugs for the treatment of malaria

Tablets , sulfadoxine 500 mg with pyrimethamine 25 mg

Uses:

treatment of malaria due to susceptible *P. falciparum* in areas of high chloroquine resistance and in patients who have not responded to chloroquine; additionally quinine may be given for 3 days (see notes above)

Contraindications:

hypersensitivity to sulfonamides or pyrimethamine; severe hepatic or renal impairment (except where no alternative treatment available)

Precautions:

avoid in blood disorders—unless specialist supervision; 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); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Treatment of malaria due to susceptible *P. falciparum* (see notes above), *by mouth* , **ADULT** sulfadoxine 1.5 g with pyrimethamine 75 mg (3 tablets) as a single dose; **CHILD** 5–10 kg, half tablet; 11–20 kg, 1 tablet; 21–30 kg, 1½ tablets; 31–45 kg, 2 tablets, as a single dose

Adverse effects:

rashes, pruritus, slight hair loss; rarely erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis; gastrointestinal disturbances including nausea, vomiting, stomatitis; rarely, hepatitis, leukopenia, thrombocytopenia, megaloblastic anaemia and purpura—withdraw treatment; fatigue, headache, fever, polyneuritis, also reported; pulmonary infiltrates such as eosinophilic or allergic alveolitis—if symptoms of cough or shortness of breath—withdraw treatment

Antitrypanosomal drugs

African trypanosomiasis

African trypanosomiasis, or sleeping sickness, is a protozoan infection 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. b. rhodesiense* infection but only after several months or years in *T. b. gambiense* infection.

Treatment of early-stage infections of *T. b. rhodesiense* with **suramin sodium** and *T. b. gambiense* with **pentamidine isetionate** 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. b. gambiense* infection. **Melarsoprol** is used for confirmed cases of *T. b. gambiense* or *T. b. rhodesiense* with meningoencephalitic involvement. 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 (especially for children and debilitated patients), increasing to a maximum of 3.6 mg/kg daily. It is given in short courses of 3–4 days with an interval of 7–10 days between courses. A severe febrile reaction may occur after the first injection, especially if patients have a large number of trypanosomes in their blood; therefore, suramin or pentamidine are often given before starting melarsoprol treatments. An increasing number of melarsoprol treatment failures have been reported in the last years in several countries. **Eflornithine** is an alternative drug which has been shown to be both effective and considerably less toxic than melarsoprol in patients with meningoencephalopathy resulting from *T. b. gambiense* trypanosomiasis.

Melarsoprol

Injection (Solution for injection), melarsoprol 3.6% in propylene glycol

Uses:

treatment of meningoencephalitic stage of *T. b. gambiense* or *T. b. rhodesiense* infections

Contraindications:

pregnancy; avoid use during influenza epidemics

Precautions:

hospitalization and close medical supervision required throughout treatment; episodes of reactive encephalopathy (may require treatment suspension); treat intercurrent infections such as pneumonia and malaria before malarsoprol administration; malnutrition (if possible, correct with protein-rich diet); G6PD deficiency; leprosy—may precipitate erythema nodosum

Dosage:

Treatment of *T. b. gambiense* and *T. b. rhodesiense* with meningoencephalitic involvement (see notes 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 *or* 2.2 mg/kg daily for 10 days

ADMINISTRATION. Injection very irritant—avoid extravasation. Patients should remain supine and fasting for at least 5 hours after injection

Adverse effects:

fatal reactive encephalopathy characterized by headache, tremor, slurred speech, convulsions and ultimately coma (in 3–8% of patients, usually at end of 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—in late stage of treatment

Pentamidine isetionate

Pentamidine isetionate is a complementary antitrypanosomal drug

Injection (Powder for solution for injection), pentamidine isetionate 200-mg vial, 300-mg vial

Uses:

treatment of haemolymphatic stage of *T. b. gambiense* infection; adjunct to melarsoprol in meningoencephalitic stage of *T. b. gambiense* infection; leishmaniasis (section 6.4.2); *Pneumocystis carinii* pneumonia (section 6.4.5)

Contraindications:

severe renal impairment; *T. b. rhodesiense* infection (since primary resistance observed)

Precautions:

cerebrospinal fluid examination before treatment (pentamidine not likely to be effective if leukocyte count greater then 5 cells/mm^3 , total protein greater then 37 mg/100 ml, or trypanosomes 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; hypoglycaemia or hyperglycaemia; leukopenia; thrombocytopenia; anaemia; immunodeficiency—if acute deterioration in bone marrow, renal or pancreatic function, interrupt or discontinue treatment; renal impairment (Appendix 4); pregnancy—should not be withheld, even if evidence of meningoencephalitic

involvement, as melarsoprol contraindicated (Appendix 2); breastfeeding (Appendix 3)

Dosage:

Treatment of haemolymphatic stage of *T. b. 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. b. 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 isetionate is toxic; care is required 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, Stevens-Johnson syndrome reported; pain, local induration, sterile abscess and muscle necrosis at injection site

Suramin sodium

Injection (Powder for solution for injection), suramin sodium 1-g vial

Uses:

treatment of haemolymphatic stage of *T. b. gambiense* and *T. b. rhodesiense* infections; adjunct to melarsoprol in meningoencephalitic stage of *T. b. gambiense* and *T. b. rhodesiense* infections; onchocerciasis (section 6.1.2.3)

Contraindications:

previous anaphylaxis or suramin sensitivity; severe liver or renal function impairment; elderly or debilitated

Precautions:

administer only under close medical supervision in hospital and with general condition improved as far as possible before treatment; first dose—possible loss of consciousness (see under Dosage, 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—should not be withheld, even if evidence of meningoencephalitic involvement, as melarsoprol contraindicated

Dosage:

Treatment of haemolymphatic *T. b. gambiense* and *T. b. rhodesiense* 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

Treatment of meningoencephalitic *T. b. gambiense* and *T. b. rhodesiense* infections (prior to melarsoprol), *by slow intravenous injection* , **ADULT** and **CHILD** 5 mg/kg on day 1, 10 mg/kg on day 3 and in some regimens, 20 mg/kg on day 5

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 next 0.5 ml over 30 seconds and wait one 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 First (Test) Dose, 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

Eflornithine hydrochloride

Eflornithine hydrochloride is a complementary drug

Infusion (Solution for dilution for infusion), eflornithine hydrochloride 200 mg/ml, 100-ml ampoule

Uses:

treatment of haemolymphatic and meningoencephalitic stages of *T. b. gambiense* infection

Contraindications:

pregnancy; breastfeeding

Precautions:

hospitalization and close supervision throughout treatment; blood and lymph node aspirates examined daily until trypanosome negative for two consecutive days, then weekly during treatment; examination for leukocytes, total protein content and trypanosome presence in CSF after course of treatment and at intervals for following 24 months; renal impairment (Appendix 4)

Dosage:

Treatment of *T. b. gambiense* infections, *by intravenous infusion,* **ADULT** 100 mg/kg over 45 minutes, every 6 hours for at least 14 days (7 days if previous treatment with melarsoprol has failed); if relapse occurs, repeat course of treatment

DILUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects:

diarrhoea, anaemia, leukopenia, thrombocytopenia and convulsions; impaired hearing reported; vomiting, anorexia, alopecia, abdominal pain, headache, facial oedema, eosinophilia and dizziness—less common and reversible on treatment withdrawal

American trypanosomiasis

American trypanosomiasis (Chagas disease) is caused by the protozoan parasite *Trypanosoma cruzi* which are carried by reduviid or triatomine bugs which 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 drugs in pregnancy has not been established and treatment should be deferred until after the first trimester. They 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

Tablets , benznidazole 100 mg

Uses:

acute American trypanosomiasis (Chagas disease)

Contraindications:

early pregnancy

Precautions:

hepatic, renal or haematological insufficiency—require close medical supervision; monitor blood count, especially leukocytes, throughout treatment

Dosage:

Acute American trypanosomiasis (Chagas disease), *by mouth* , **ADULT** 5–7 mg/kg daily in two divided doses for 60 days; **CHILD** up to 12 years 10 mg/kg daily in two divided doses for 60 days

Adverse effects:

rashes—if severe and accompanied by fever and purpura, discontinue treatment; nausea, vomiting and abdominal pain; dose-related paraesthesia and peripheral neuritis—discontinue treatment; leukopenia and rarely, agranulocytosis

Nifurtimox

Tablets , nifurtimox 30 mg, 120 mg, 250 mg

Uses:

acute American trypanosomiasis (Chagas disease)

Contraindications:

early pregnancy

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

Dosage:

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, convulsions—dose-related, reduce dose; peripheral neuritis—may require discontinuation; rashes and other allergic reactions

Antipneumocystosis and antitoxoplasmosis drugs

PNEUMOCYSTOSIS

Pneumocystis carinii is classified as a protozoan although there is evidence to suggest that it is probably a fungus. *Pneumocystis carinii* 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 with **trimethoprim** is the treatment of choice for *Pneumocystis carinii* pneumonia and is also used for prophylaxis in high-risk patients; **pentamidine isetionate** is used in patients unresponsive to or intolerant of sulfamethoxazole with trimethoprim.

The treatment of *Pneumocystis carinii* infections must only be undertaken with specialist supervision 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 occurs in AIDS) in a previously infected person, may result in encephalitis or meningoencephalitis. 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. Ocular toxoplasmosis causes chorioretinitis and is often the result of a childhood infection that becomes apparent in adulthood.

The treatment of choice for toxoplasmosis is **pyrimethamine** with **sulfadiazine** ; a folate supplement is also given to counteract the megaloblastic anaemia associated with these drugs.

Sulfamethoxazole with trimethoprim

Tablets , sulfamethoxazole 400 mg with trimethoprim 80 mg; sulfamethoxazole 800 mg with trimethoprim 160 mg

Oral suspension , sulfamethoxazole 200 mg with trimethoprim 40 mg/5 ml

Injection (Solution for dilution for infusion), sulfamethoxazole 80 mg with trimethoprim 16 mg/ml, 5-ml and 10-ml ampoules

Uses:

Pneumocystis carinii pneumonia; bacterial infections (section 6.2.2.9)

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; avoid in blood disorders (unless under specialist supervision); monitor blood counts and discontinue

immediately if blood disorder develops; rash—discontinue immediately; predisposition to folate deficiency; elderly; asthma; G6PD deficiency; pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Treatment of *Pneumocystis carinii* pneumonia (see notes above), *by mouth or by intravenous infusion* , **ADULT** and **CHILD** sulfamethoxazole up to 100 mg/kg daily with trimethoprim up to 20 mg/kg daily in 2–4 divided doses for 14–21 days

Prophylaxis of *Pneumocystis carinii* pneumonia (see notes above), *by mouth* , **ADULT** and **CHILD** sulfamethoxazole 25 mg/kg with 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 rashes, 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, anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, purpura—discontinue immediately; also reported, 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; megaloblastic anaemia due to trimethoprim

Pentamidine isetionate

Pentamidine isetionate is a complementary antipneumocystosis drug

Injection (Powder for solution for injection), pentamidine isetionate 200-mg vial, 300-mg vial

Nebulizer solution , pentamidine isetionate 300-mg bottle [not included on WHO Model List]

Uses:

Pneumocystis carinii pneumonia; leishmaniasis (section 6.4.2); African trypanosomiasis (section 6.4.4.1)

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; renal impairment (Appendix 4); leukopenia, thrombocytopenia, anaemia; immunodeficiency—if acute deterioration in bone marrow, renal or pancreatic function, interrupt or discontinue treatment; pregnancy—in potentially fatal *P. carinii* pneumonia, treat without delay (Appendix 2); breastfeeding (Appendix 3); carry out laboratory monitoring according to manufacturer's literature

Dosage:

Treatment of *P. carinii* pneumonia (see notes above), *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* pneumonia (see notes above), *by slow intravenous infusion* , **ADULT** and **CHILD** 4 mg/kg once every 4 weeks *or 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 isetionate is toxic; care is required 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, Stevens-Johnson syndrome reported; pain, local induration, sterile abscess and muscle necrosis at injection site

Pyrimethamine

Tablets , pyrimethamine 25 mg, 50 mg [50-mg strength not included on WHO Model List]

Uses:

toxoplasmosis (with sulfadiazine); malaria (with sulfadoxine) (section 6.4.3)

Contraindications:

hepatic and renal impairment

Precautions:

pregnancy (avoid in first trimester but give in later pregnancy if danger of congenital transmission; Appendix 2); breastfeeding (Appendix 3); blood counts required with prolonged treatment; folate supplements throughout treatment; **interactions:** Appendix 1

Dosage:

Toxoplasmosis (in second and third trimesters of pregnancy), *by mouth* , **ADULT** 25 mg daily for 3–4 weeks

Toxoplasmosis in neonates, *by mouth* , **neonate** 1 mg/kg daily; duration of treatment depends on whether neonate has overt disease—continue for 6 months, or is without overt disease but, born to mother infected during pregnancy—treat for 4 weeks, followed by further courses if infection confirmed

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 (see below)

Adverse effects:

depression of haematopoiesis with high doses; megaloblastic anaemia; rashes; insomnia; gastrointestinal disturbances

Sulfadiazine

Sulfadiazine is a complementary antitoxoplasmosis drug

Tablets , sulfadiazine 500 mg

Uses:

toxoplasmosis (with pyrimethamine); rheumatic fever (section 6.2.2.9)

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); avoid in blood disorders (unless under specialist supervision); monitor blood counts and discontinue immediately if blood disorder develops; rashes—discontinue immediately;

predisposition to folate deficiency; elderly; asthma; G6PD deficiency; pregnancy—avoid in first trimester, but may be given thereafter if danger of congenital transmission (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Toxoplasmosis (in second and third trimesters of pregnancy), *by mouth* , **ADULT** 3 g daily in 4 divided doses

Toxoplasmosis in neonates, *by mouth* , **neonate** 85 mg/kg daily in 2 divided doses; duration of treatment depends on whether the neonate has overt disease—continue for 6 months, or is without overt disease but born to mother infected during pregnancy—treat for 4 weeks, followed by further courses, if infection confirmed

Toxoplasmosis in immunodeficiency, *by mouth* , **ADULT** 4–6 g daily in 4 divided doses for at least 6 weeks, followed by a suppressive dose of 2–4 g daily

Chorioretinitis, *by mouth* , **ADULT** 2 g daily in 4 divided doses

NOTE. For the treatment of toxoplasmosis, sulfadiazine must always be taken with pyrimethamine (see above)

Adverse effects:

nausea, vomiting, diarrhoea, headache; hypersensitivity reactions including rashes, 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, anuria; blood disorders including granulocytopenia, agranulocytosis, aplastic anaemia, purpura—discontinue immediately; also reported, 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

Antiviral drugs

Herpes and cytomegalovirus infections

HERPES SIMPLEX VIRUS (HSV)

Aciclovir is active against herpes viruses but does not eradicate them. It is only effective if started at 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. HSV encephalitis or pneumonitis should be treated with intravenous aciclovir.

Valaciclovir [not included on 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).

HERPES ZOSTER VIRUS

While most HIV positive patients with zoster experience only one self-limiting course, some will experience repeated episodes. Treatment should be reserved for debilitating disease and when there is high risk of serious complications, such as in advanced HIV disease. Aciclovir is the treatment of choice and it can be administered in high oral dose or in the case of lack of response to oral therapy or CNS involvement, it should be given intravenously.

CYTOMEGALOVIRUS (CMV)

Parenteral antiviral **ganciclovir** arrests retinochoroiditis and enteritis caused by CMV in HIV infected patients. Maintenance therapy with oral ganciclovir should be given to prevent relapse of retinitis. Alternative therapy with intravenous **foscarnet** can be used if necessary.

Aciclovir

Aciclovir is a representative drug active against herpes simplex virus and varicella–zoster virus. Various drugs can serve as alternatives

Tablets , aciclovir 200 mg

Oral suspension , aciclovir 200 mg/5 ml [not included on WHO Model List]

Infusion (Powder for solution for infusion), aciclovir (as sodium salt) 250-mg vial

Uses:

treatment of primary genital herpes; disseminated varicella–zoster in immunocompromised patients; herpes simplex encephalitis

Precautions:

maintain adequate hydration; renal impairment (Appendix 4); pregnancy (Appendix 2); breastfeeding (Appendix 3)

Dosage:

Treatment of primary genital herpes, *by mouth* , **ADULT** 200 mg 5 times daily for 7–10 days *or* 400 mg 3 times daily for 7–10 days

Prevention of recurrence of genital herpes, *by mouth* , **ADULT** 400 mg twice daily

Disseminated varicella–zoster in immunocompromised patients, *by intravenous infusion* , **ADULT** 10 mg/kg 3 times daily for 7 days

Herpes simplex encephalitis, *by intravenous infusion* , **ADULT** 10 mg/kg 3 times daily for 10 days

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects:

nausea, vomiting, abdominal pain, diarrhoea, headache, fatigue, rash, urticaria, pruritus, photosensitivity; rarely hepatitis, jaundice, dyspnoea, angioedema, anaphylaxis; neurological reactions (including dizziness, confusion, hallucinations, drowsiness), acute renal failure; decreases in haematological indices; on intravenous infusion, severe local inflammation (sometimes resulting in ulceration), fever, agitation, tremor, psychosis, and convulsions

Antiretroviral drugs

Antiretroviral drugs do not cure HIV (human immunodeficiency virus) 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 drugs. 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. The use of fixed-dose preparations for these combinations is also 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 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 as a drug in its own right.

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 before the immune system is irreversibly damaged. 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 take into account convenience and the patient's tolerance of it. 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. Testing for resistance to antiviral drugs, particularly in therapeutic failure, should be considered.

Women of childbearing age receiving antiretroviral therapy must have available 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** , **lamivudine** , **stavudine** , and zalcitabine.

The protease inhibitors include amprenavir, **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 it increases the antiviral activity of the other protease inhibitors by reducing their 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 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. Efavirenz treatment has also been associated with an increased plasma cholesterol concentration.

INITIATION OF TREATMENT

The time for initiating antiviral treatment is determined by the clinical stage of the HIV infection as indicated by symptoms, and where available, by the CD4-cell count or total lymphocyte count; the plasma viral load, if available, is also a valuable guide for staging the disease (see Monitoring, below).

Recommended initial treatment with a combination of drugs ('highly active antiretroviral therapy', HAART) includes:

2 nucleoside reverse transcriptase inhibitors (section 6.5.2.1)

plus

a non-nucleoside reverse transcriptase inhibitor (section 6.5.2.2)

or a third nucleoside reverse transcriptase inhibitor (section 6.5.2.1)

or a protease inhibitor which may be combined with ritonavir as booster (section 6.5.2.3).

MONITORING

In resource-limited settings the basic clinical assessment before initiating antiretroviral therapy includes 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 current symptoms and physical signs.

The *absolute minimum laboratory tests* 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 neutrophils and the possibility of neutropenia);
- total lymphocyte count;
- serum alanine or aspartate aminotransferase concentration to assess the possibility of hepatitis co-infection and to monitor for hepatotoxicity;
- serum creatinine and/or blood urea nitrogen to assess baseline renal function;
- serum glucose;
- pregnancy tests for women.

Desirable supplemental tests include measurement of bilirubin, amylase and serum lipids. CD4-cell determinations are, of course, very desirable and efforts should be made to make these widely available. Viral load testing is currently considered optional because of constraints on resources.

CHANGING THERAPY

Deterioration of the condition (including clinical and virological changes) usually calls for replacement of the failing drugs. Intolerance to adverse effects and drug-induced organ dysfunction usually require 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, either a new second-line regimen is indicated or, if the toxicity is related to an identifiable drug in the regimen, the offending drug can be replaced with another drug that does not have the same adverse effects.

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 drugs 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.

The use of zidovudine, lamivudine, nevirapine, nelfinavir and saquinavir are recommended for women of child-bearing potential or who are pregnant. Efavirenz should be avoided because of its potential teratogenic effect on the fetus in the first trimester. First-line treatment in pregnant women should when possible include zidovudine and lamivudine. Monotherapy with either zidovudine or with nevirapine reduces transmission of infection to the neonate (see also below), but combination antiretroviral therapy maximizes the chance of preventing transmission and represents optimal therapy for the mother. Low-dose ritonavir is required if either indinavir or saquinavir is used in pregnancy because adequate drug concentration is achieved only with ritonavir boosting. Information is lacking on the use of lopinavir with ritonavir in pregnancy.

Lactic acidosis and hepatic steatosis associated with nucleoside reverse transcriptase inhibitors may be more frequent in pregnant women and therefore the combination of stavudine and didanosine should 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 they occur.

Various regimens have been used to specifically prevent the transmission of HIV from mother to the neonate at term. More information is available in *New Data on the Prevention of Mother-to-Child Transmission of HIV and their Policy Implications: Conclusions and Recommendations* (WHO/RHR/01.28), which reflects an inter-agency consultation held on 11–13 October 2000.

BREASTFEEDING

Antiretroviral drugs may be present in breastmilk, and may reduce viral load in breastmilk and reduce the risk of transmission through breastfeeding. However, the concentration of antiretroviral drugs in breastmilk 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, where possible, they should limit or avoid breastfeeding; in particular, breastfeeding should be avoided where replacement feeding is acceptable, affordable, sustainable, and safe. HIV-infected women should be counselled on infant feeding options and they should be supported in their choice.

POST-EXPOSURE PROPHYLAXIS

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

LIPODYSTROPHY AND METABOLIC EFFECTS

Combination antiretroviral therapy, including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients (for example, decreased fat under the skin, increased abdominal fat, 'buffalo humps' and breast enlargement). Protease inhibitors are also associated with metabolic abnormalities such as hyperlipidaemia, insulin resistance, and hyperglycaemia. Clinical examination should include an evaluation of fat distribution; measurement of serum lipids and blood glucose should be considered.

Nucleoside reverse transcriptase inhibitors

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

Abacavir

ABC

Tablets , abacavir (as sulfate) 300 mg

Oral solution , abacavir (as sulfate) 100 mg/5 ml

Uses:

HIV infection in combination with at least two other antiretroviral drugs

Precautions:

hepatic impairment (see below and Appendix 5); renal impairment (Appendix 4); pregnancy (see notes above and Appendix 2); breastfeeding (see notes above)

HYPERSENSITIVITY REACTIONS.	Life-threatening hypersensitivity reactions reported—characterized by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, lethargy, malaise, headache, myalgia and renal failure; less frequently mouth ulceration, oedema, hypotension, dyspnoea, sore throat, cough, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia and anaphylaxis (hypersensitivity reactions presenting as sore throat, influenza-like illness, cough and breathlessness identified); rarely myolysis; laboratory abnormalities may include raised liver enzymes (see below) and creatine kinase; symptoms usually appear in the first 6 weeks, but may occur at any time; monitor for symptoms every 2 weeks for 2 months; discontinue immediately if any symptom of hypersensitivity develops and do not rechallenge (risk of more severe hypersensitivity reaction); discontinue if hypersensitivity cannot be ruled out, even when other diagnoses possible—if rechallenge necessary it

must be carried out in hospital setting; if abacavir is stopped for any reason other than hypersensitivity, exclude hypersensitivity reaction as the cause and rechallenge only if medical assistance is readily available; care needed with concomitant use of drugs which cause skin toxicity

Patient Advice. Patients should be told the importance of regular dosing (intermittent therapy may increase sensitization), how to recognize signs of hypersensitivity, and advised to seek immediate medical attention if symptoms develop or before re-starting treatment

HEPATIC DISEASE. Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported—caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis

Dosage:

HIV infection (in combination with other antiretroviral drugs), *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 (see above), nausea, vomiting, diarrhoea, anorexia, lethargy, fatigue, fever, headache, pancreatitis, lactic acidosis (see hepatic disease, above); rash and gastrointestinal disturbances more common in children

Didanosine

ddI, DDI

Chewable tablets , didanosine (with calcium and magnesium antacids) 25 mg, 50 mg; 100 mg, 150 mg, 200 mg

Oral solution (Powder for oral solution), didanosine (with calcium and magnesium antacids) 100 mg/sachet, 167 mg/sachet, 250 mg/sachet

Enteric-coated capsules (Gastro-resistant capsules), didanosine 125 mg, 200 mg, 250 mg, 400 mg

NOTE. Antacids in formulation may affect absorption of other drugs—see **interactions:** Appendix 1 (antacids)

Uses:

HIV infection in combination with at least two other antiretroviral drugs

Precautions:

history of pancreatitis (preferably avoid, otherwise extreme caution, see also below); peripheral neuropathy or hyperuricaemia (see under Adverse effects); history of liver disease (see below); renal and hepatic impairment (see Appendices 4 and 5); pregnancy and breastfeeding (see notes above); 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 asymptomatic) suspend treatment until diagnosis of pancreatitis excluded; on return to normal values re-initiate treatment only if essential (using low dose increased gradually if appropriate). Whenever possible avoid concomitant treatment with other drugs known to cause pancreatic toxicity (for example intravenous pentamidine isetionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis monitor closely if elevated

HEPATIC DISEASE. Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease, excessive alcohol intake, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis

Dosage:

HIV infection (in combination with other antiretroviral drugs), *by mouth* , **ADULT** under 60 kg 250 mg daily in 1–2 divided doses, body weight over 60 kg 400 mg daily in 1–2 divided doses; **CHILD** under 3 months, 50 mg/m^2 twice daily; 3 months–13 years, 90 mg/m^2 twice daily *or* 240 mg/m^2 once daily

Patient Advice. To ensure sufficient antacid from tablets containing antacid, 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 (reduced dose may be tolerated when symptoms resolve); hyperuricaemia (suspend treatment if significant elevation); diarrhoea (occasionally serious); also reported, nausea, vomiting, dry mouth, asthenia, headache, hypersensitivity reactions, retinal and optic nerve changes (especially in children), diabetes mellitus, raised liver enzymes (see also under Precautions), liver failure

Lamivudine

3TC

Tablets , lamivudine 150 mg

Oral solution , lamivudine 50 mg/5 ml

Uses:

HIV infection in combination with at least two other antiretroviral drugs

Precautions:

renal impairment (Appendix 4), hepatic disease (see below); pregnancy and breastfeeding (see notes above); **interactions:** Appendix 1

HEPATIC DISEASE. Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution (particularly in obese women) in liver disease, liver enzyme abnormalities, or risk factors for liver disease; suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis. Recurrent hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine

Dosage:

HIV infection (in combination with other antiretroviral drugs), *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)

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

d4T

Capsules , stavudine 15 mg, 20 mg, 30 mg, 40 mg

Oral solution (Powder for oral solution), stavudine 5 mg/5 ml

Uses:

HIV infection in combination with at least two other antiretroviral drugs

Precautions:

history of peripheral neuropathy (see below); history of pancreatitis or concomitant use with other drugs associated with pancreatitis; hepatic disease (see below); renal impairment (Appendix 4); pregnancy and breastfeeding (see notes above); **interactions:** Appendix 1

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

HEPATIC DISEASE. Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic

acidosis

Dosage:

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

Adverse effects:

peripheral neuropathy (dose-related, see above); pancreatitis; nausea, vomiting, diarrhoea, constipation, anorexia, abdominal discomfort; chest pain; dyspnoea; headache, dizziness, insomnia, mood changes; asthenia, musculoskeletal pain; influenza-like symptoms, rash and other allergic reactions; lymphadenopathy; neoplasms; elevated liver enzymes (see hepatic disease, above) and serum amylase; neutropenia, thrombocytopenia

Zidovudine

Azidothymidine, AZT, ZDV

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

Capsules , zidovudine 100 mg, 250 mg

Tablets , zidovudine 300 mg

Syrup (Oral solution), zidovudine 50 mg/5 ml

Infusion (Concentrate for solution for infusion), zidovudine 10 mg/ml, 20-ml vial

Uses:

HIV infection in combination with at least two other antiretroviral drugs; monotherapy for prevention of maternal-fetal HIV transmission (but see notes above under Pregnancy)

Contraindications:

abnormally low neutrophil counts or haemoglobin (consult product literature); neonates either with hyperbilirubinaemia requiring treatment other than phototherapy or with raised transaminase (consult product literature)

Precautions:

haematological toxicity; vitamin B_{12} deficiency (increased risk of neutropenia); reduce dose or interrupt treatment according to product literature if anaemia or myelosuppression; renal impairment (Appendix 4); hepatic impairment (see below

and Appendix 5); risk of lactic acidosis, (see below); elderly; pregnancy and breastfeeding (see notes above); **interactions:** Appendix 1

HEPATIC DISEASE. Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported therefore caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women), suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis

Dosage:

HIV infection (in combination with other antiretroviral drugs), *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

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** 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 maternal-fetal HIV transmission, see notes above under Pregnancy

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 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

Non-nucleoside reverse transcriptase inhibitors

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

Efavirenz

EFV, EFZ

Capsules , efavirenz 50 mg, 100 mg, 200 mg

Oral solution , efavirenz 150 mg/5 ml

Uses:

HIV infection in combination with at least two other antiretroviral drugs

Contraindications:

pregnancy (see notes above and Appendix 2; substitute nevirapine for efavirenz in pregnant women or women for whom effective contraception cannot be assured)

Precautions:

hepatic impairment (avoid if severe; Appendix 5); severe renal impairment (Appendix 4); breastfeeding (see notes above); elderly; history of mental illness or substance abuse; **interactions:** Appendix 1

RASH. Rash, usually in the first 2 weeks, is the most common adverse effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption—rash usually resolves within 1 month

Dosage:

HIV infection (in combination with other antiretroviral drugs), *by mouth* , **ADULT** 600 mg once daily; **CHILD** over 3 years, body weight 10–15 kg, 200 mg once daily; body weight 15–19 kg, 250 mg once daily; body weight 20–24 kg, 300 mg once daily; body weight 25–32 kg, 350 mg once daily; body weight 33–39 kg, 400 mg once daily; body weight 40 kg and over, adult dose

Adverse effects:

rash including Stevens-Johnson syndrome (see also above); dizziness, headache, insomnia, somnolence, abnormal dreams, fatigue, impaired concentration (administration at bedtime especially in the first 2–4 weeks reduces CNS effects); nausea; less frequently vomiting, diarrhoea, hepatitis, depression, anxiety, psychosis, amnesia, ataxia, stupor, vertigo; also reported raised serum cholesterol, elevated liver enzymes (especially if seropositive for hepatitis B or C), pancreatitis

Nevirapine

NVP

Tablets , nevirapine 200 mg

Oral suspension , nevirapine 50 mg/5 ml

Uses:

HIV infection, in combination with at least two other antiretroviral drugs; prevention of mother-to-child transmission in HIV-infected patients (but see notes above under Pregnancy)

Precautions:

hepatic impairment (see below and Appendix 5); history of chronic hepatitis (greater risk of hepatic adverse effects), pregnancy and breastfeeding (see notes above); **interactions:** Appendix 1

HEPATIC DISEASE. Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually occurring in first 8 weeks; monitor liver function before long-term treatment then every 2 weeks for 2 months then after 1 month and then every 3–6 months; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction—discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate abnormalities in liver function tests with no hypersensitivity reaction

RASH. Rash, usually in first 8 weeks, is most common adverse effect; incidence reduced if introduced at low dose and dose increased gradually; discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, swelling, general malaise or hypersensitivity reactions; if rash mild or moderate may 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 seek immediate medical attention if symptoms develop

Dosage:

HIV infection (in combination with other antiretroviral drugs), *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 twice daily for first 14 days, then (if no rash present) 200 mg/m^2 twice daily

Prevention of mother-to-child transmission of HIV (see also notes 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

NOTE. If treatment interrupted for more than 7 days reintroduce with 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 Precautions above); hepatitis or jaundice reported (see also Precautions above); nausea, vomiting, abdominal pain, diarrhoea, headache, drowsiness, fatigue, fever; hypersensitivity reactions (may involve hepatic reactions and rash, see Precautions above); anaphylaxis, angioedema, urticaria also reported

Protease inhibitors

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

Indinavir

IDV

Capsules , indinavir (as sulfate) 200 mg, 333 mg, 400 mg

Uses:

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

Precautions:

hepatic impairment (Appendix 5); ensure adequate hydration to reduce risk of nephrolithiasis; diabetes mellitus; haemophilia; pregnancy (see notes above and Appendix 2); breastfeeding (see notes above); metabolism of many drugs inhibited if administered concomitantly; **interactions:** Appendix 1

Dosage:

HIV infection (in combination with nucleoside reverse transcriptase inhibitors and low-dose ritonavir booster), *by mouth* , **ADULT** indinavir 800 mg and ritonavir 100 mg both twice daily

HIV infection (in combination with nucleoside reverse transcriptase inhibitors but without 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 low-fat, light meal; when given with didanosine tablets, allow 1 hour between the drugs (antacids in didanosine reduce absorption of indinavir)

Adverse effects:

nausea, vomiting, diarrhoea, abdominal discomfort, dyspepsia, flatulence, pancreatitis, dry mouth, taste disturbances; headache, dizziness, insomnia; myalgia, myositis, rhabdomyolysis, asthenia, hypoaesthesia, paraesthesia; hyperglycaemia;

anaphylactoid 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, haemolytic anaemia; lipodystrophy and metabolic effects, see notes above

Lopinavir with ritonavir

LPV/r

Capsules , lopinavir 133.3 mg and ritonavir 33.3 mg

Oral solution , lopinavir 400 mg and ritonavir 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 two other antiretroviral drugs

NOTE. Ritonavir increases effect of lopinavir (see notes above); low dose in combination does not have intrinsic antiviral activity

Precautions:

hepatic impairment—avoid if severe (Appendix 5); renal impairment (Appendix 4); haemophilia; pregnancy (see notes above and Appendix 2); breastfeeding (see notes above and 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; **interactions:** Appendix 1

PANCREATITIS. Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated—discontinue if pancreatitis diagnosed

Dosage:

HIV infection (in combination with other antiretroviral drugs), *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 and ritonavir 100 mg twice daily); **CHILD** 6 months–13 years, lopinavir 225 mg/m^2 and ritonavir 57.5 mg/m^2 twice daily (*or* body weight 7–15 kg lopinavir 12 mg/kg and ritonavir 3 mg/kg twice daily, body weight 15–40 kg lopinavir 10 mg/kg and ritonavir 5 mg/kg twice daily)

NOTE. Increase dose by 33% if used with efavirenz or with nevirapine

Patient Advice. Each dose to be taken with food

Adverse effects:

diarrhoea, nausea, vomiting, colitis, abdominal discomfort, asthenia, headache, insomnia; rash; less frequently, dry mouth, hepatic dysfunction, pancreatitis (see also Precautions), dyspepsia, dysphagia, oesophagitis, influenza-like syndrome, appetite changes; hypertension, palpitations, thrombophlebitis, vasculitis, chest pain, dyspnoea, agitation, anxiety, ataxia, hypertonia, confusion, depression, dizziness, dyskinesia, paraesthesia, peripheral neuritis, somnolence; Cushing syndrome, hypothyroidism, sexual dysfunction, anaemia, leukopenia, dehydration, oedema, lactic acidosis; arthralgia, myalgia, abnormal vision, otitis media, taste disturbances, tinnitus; acne, alopecia, dry skin, pruritus, skin discoloration, nail disorders, sweating; lipodystrophy and metabolic effects (see notes above); raised bilirubin and lowered sodium, low platelet and low neutrophil counts also reported in children

Nelfinavir

NFV

Tablets , nelfinavir (as mesilate) 250 mg

Oral powder , nelfinavir (as mesilate) 50 mg/g

Uses:

HIV infection in combination with two other antiretroviral drugs

Precautions:

hepatic and renal impairment; diabetes mellitus; haemophilia; pregnancy and breastfeeding (see notes above); **interactions:** Appendix 1

Dosage:

HIV infection (in combination with other antiretroviral drugs), *by mouth* , **ADULT** 1.25 g twice daily *or* 750 mg 3 times daily; **CHILD** under 1 year, 40–50 mg/kg 3 times daily *or* 65–75 mg/kg twice daily; 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; reports of elevated creatine kinase, hepatitis, pancreatitis, neutropenia, hypersensitivity reactions including bronchospasm, fever, pruritus and facial oedema, lipodystrophy and metabolic effects, see notes above

Ritonavir

r, RTV

Capsules , ritonavir 100 mg

Oral solution , ritonavir 400 mg/5 ml

Uses:

HIV infection, as a booster to increase effect of indinavir, lopinavir or saquinavir and in combination with two other antiretroviral drugs

Contraindications:

severe hepatic impairment

Precautions:

hepatic impairment; diabetes mellitus; haemophilia; pregnancy and breastfeeding (see notes above); **interactions:** Appendix 1

PANCREATITIS. Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated—discontinue if pancreatitis diagnosed

Dosage:

HIV infection (as a booster with other antiretroviral drugs), *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; headache, circumoral and peripheral paraesthesia, hyperaesthesia, dizziness, sleep disturbances, asthenia, rash, hypersensitivity reactions, leukopenia; raised liver enzymes, bilirubin, and uric acid; occasionally flatulence, eructation, dry mouth and ulceration, cough, anxiety, fever, pain, myalgia, weight loss, decreased thyroxine, sweating, pruritus, electrolyte disturbances, anaemia, neutropenia, increased prothrombin time; pancreatitis (see also Pancreatitis, above); lipodystrophy and metabolic effects, see notes above

Saquinavir

SQV

Capsules (gel-filled), saquinavir 200 mg

Uses:

HIV infection in combination with two other antiretroviral drugs and usually with low-dose ritonavir booster

Contraindications:

severe hepatic impairment (Appendix 5)

Precautions:

hepatic impairment (Appendix 5); renal impairment (Appendix 4); diabetes mellitus; haemophilia; pregnancy and breastfeeding (see notes above); **interactions:** Appendix 1

Dosage:

HIV infection (in combination with nucleoside reverse transcriptase inhibitors and low-dose ritonavir booster), *by mouth* , **ADULT** saquinavir 1 g and ritonavir 100 mg twice daily

HIV infection (in combination with other antiretroviral drugs but without 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; headache, peripheral neuropathy, paraesthesia, dizziness, insomnia, mood changes, ataxia, musculoskeletal pain, asthenia; fever, pruritus, rash and other skin eruptions, rarely Stevens-Johnson syndrome; other rare adverse effects include 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 notes above)

Insect repellents

Diethyltoluamide , an effective insect repellent, is used for the prevention of infections transmitted by insect bites, ticks, harvest mites and fleas. One application offers protection for 4 to 8 hours.

Diethyltoluamide

Cutaneous solution , diethyltoluamide 50%, 75%

Uses:

insect repellent against mosquitoes, biting flies, ticks, harvest mites and fleas

Precautions:

avoid contact with eyes or mouth, mucous membranes, areas of flexures, wounds, broken or irritated skin

Administration:

Apply sparingly to exposed skin and when treatment no longer needed, wash skin thoroughly with soap and water

Adverse effects:

systemic toxicity—reported with application of large topical doses, especially in children; occasionally, hypersensitivity reactions